PROFILES AND MANAGEMENT OF ADULT CANCER PATIENTS WITH NEUTROPENIA USING GRANULOCYTE COLONY STIMULATING FACTORS AT KENYATTA NATIONAL HOSPITAL

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DEDICATION

This dissertation is dedicated to my parents, Mr. Madan Mohan Singh Babra and Mrs. Rina Kaur Babra, my brother, Mr. Parmjit Singh Babra, and Leo for their unending support and encouragement throughout my life in the University.

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ASCO	American Society of Clinical Oncology
BMI	Body Mass Index
BSA	Body Surface Area
CME	Continuous Medical Education
COPD	Chronic obstructive pulmonary disease
DNA	Deoxyribonucleic acid
ESCO	European Society of Clinical Oncology
FDA	Food and Drug Administration
GCSF	Granulocyte colony-stimulating factors
GIT	Gastrointestinal tract
GMCSF	Granulocyte / Macrophage colony-stimulating factors
KNH	Kenyatta National Hospital
KNH/UoN-ERC	Kenyatta National Hospital/University of Nairobi Ethics and Research Committee
Kshs.	Kenyan shillings
MASCC	Multinational Association of Supportive Care of Cancer
NCCN	National Comprehensive Cancer Network
NHIF	National Hospital Insurance Fund
RNA	Ribonucleic acid
USA	United States of America

LIST OF FIGURES

LIST OF TABLES

OPERATIONAL DEFINITIONS

Absolute neutrophil count is defined as a quantitative measure of neutrophils in the blood. It is an indicator of the presence of infection, inflammation and other conditions.

Granulocyte colony-stimulating factor (GCSF) and Granulocyte/Macrophage colony stimulating factor (GM-CSF) are both hematopoietic growth factors that stimulate the bone marrow and causes cells to produce more granulocytes, especially neutrophils**,** or antigen presenting cells.

Neutropenia is as an absolute neutrophil count of $\leq$1.5 cells$\times 10^9$/L of blood. Kenyatta National Hospital has set this limit at <2.0cells$\times 10^9$/L of blood.

Primary neutropenia is neutropenia that is congenital and does not occur with other diseases.

Secondary neutropenia is a low neutrophil count that is associated with other causes such as autoimmune diseases, microbial diseases, malignancies, disorders of neurological origin, transplantations or with pharmacotherapy use.

Talcott's rule is a prognostic model that has been developed to predict the clinical outcomes of patients who develop neutropenia.

ABSTRACT

Background: Studies from the West have shown that patient profiles, cancer chemotherapy regimens and certain types of cancers are associated with neutropenia which is managed by granulocyte colony stimulating factors (GCSF). There is scarcity of data that characterize the profiles of patients and management of neutropenia with GCSF in resource-limited settings.

Study Objective: The study sought to characterize the profiles of adult cancer patients presenting with the neutropenia and assess its management using GCSF at Kenyatta National Hospital (KNH).

Methods: This was a cross-sectional study involving 151 eligible neutropenic participants consecutively selected from the oncology department of KNH from February 2021 to April 2021. The raw data including the patient demographics, clinical characteristics of presenting cancer, cancer treatment modalities, level of severity and management of neutropenia using GCSF were abstracted into a predesigned tool. Participants' source of funding for treatment and the handling mechanisms for GCSF were also captured.

Data Analysis: Data was analyzed using STATA statistical software 23. The Chi-square, student-T and Fisher's exact tests were used to establish the association between independent variables and the severity of neutropenia. The independent correlates for development and management of neutropenia were determined through regression analysis using forward stepwise logistic method, reporting crude and adjusted odds ratios at 95% confidence limit.

Results: The mean age of the participants was 54.2 ($\pm$12.3) years with female preponderance (71.5%). Majority of patients (30%) were in stage III, where breast (35.8%) and esophageal cancers dominated. Almost a third was in the fourth cycle where carboplatin (27.2%) and cyclophosphamide-based (25.2%) regimens were most commonly used. Patients using carboplatin-based regimens were four times more likely to develop severe neutropenia than those who did not (AOR 4.3, 95% CI 1.7-10.4, p=0.003). In addition, males were five times more likely to develop severe neutropenia compared to female counterparts (AOR 5.5, 95% CI 2.3-13.5, p<0.001) while patients with higher body surface area (BSA) were nine times more likely compared to those with small BSA (AOR 9.2, 95% CI 1.4-61.9, p=0.022). Participants undergoing concurrent chemo-radiotherapy administration were six times more likely to present

with severe neutropenia than those who did not (AOR 6.1, 95% CI 1.9-19.8, p=0.003). National Hospital Insurance Fund (NHIF) was the most commonly used source of treatment funding for GCSF but 72% of participants did not have access to cold-chain storage facilities.

Conclusion: Male gender, higher body surface area, carboplatin-based regimen and chemo-radiotherapy are significantly associated with neutropenia among cancer patients which improves upon timely administration of GCSF. NHIF was the major source of funding for treatment but handling and storage of GCSF was insufficient among participants because it was not financed.

Recommendations: Clinicians should be aware that some patient profiles such as male gender and higher body surface area as well as receiving carboplatin based chemotherapy and chemo-radiation are associated with increased risk of neutropenia. Therefore, intensification of monitoring and management of neutropenia should be directed towards these patient categories. Hospitals should encourage patients to widen their sources of funding because NHIF is not sufficient to cater for all the expenses. Large prospective studies should focus on finding out why certain clinical factors are associated with neutropenia and the trends of neutrophil counts on recommended doses of GCSF over prolonged period.

CHAPTER 1: INTRODUCTION

1.1 Epidemiology of Cancer

Cancer is an emerging health problem worldwide with an estimated total number of approximately 18 million cases and 9.5 million deaths (1). According to the Globocan 2018 Statistics in Kenya, the annual incidence of cancer is 47,887 new cases with the number of cancer related deaths accounting for 32,987 cases (2).

1.2 Management of cancer

Several studies have documented that cancer treatment modalities including surgery, cytotoxic chemotherapy, immunotherapy, radiotherapy and hormonal therapy have been researched and developed to assist in cancer management (3). The complexities involved around surgical procedures and radiotherapy has made many patients and physicians prefer cytotoxic chemotherapy which remains the standard point of care and has significantly aided in the management of the various types of cancers (4). However, cytotoxic chemotherapy targets all actively dividing cells thereby predisposing the patient to adverse effects (5). Commonly reported adverse effects of cancer chemotherapy include fatigue, hair loss, nausea, vomiting, diarrhea, mucositis, anemia and neutropenia (5). Neutropenia, particularly the febrile form, remains the most serious and life threating adverse effect of chemotherapy (5).

1.3 Chemotherapy-induced neutropenia

Chemotherapy-induced neutropenia is a decrease of neutrophil counts in blood that occurs as a result of cancer chemotherapy administration (6). Patients presenting with neutropenia in the absence of fever can lead to postponement of cancer chemotherapy administration to allow the immune system to recover and dose adjustments need to be made which may necessitate the need to change the cancer chemotherapy regimen (7). This can limit the administration of cancer chemotherapy at the required doses and on the required chemotherapy cycle thereby negatively impacting on the survival of cancer patients in the long-term with potentially curable cancers (8).

In Africa, a frequency of 30% has been reported for the development of neutropenia while the prevalence among African Americans stands at 4.4% (9). In Nigeria, a cross-sectional study conducted by Omolala, the prevalence of neutropenia amongst breast cancer patients was reported to be 31.9% (10). According to a study conducted in 2015 in Kenya with regards to the

prevalence of cancer chemotherapy-induced neutropenia amongst cancer patients, neutropenia had a prevalence of 10.5% of which severe neutropenia accounted for 6.1%, moderate were 0.6% while those with mild neutropenia attributed for 3.8% (11).

Studies have demonstrated that neutropenia can be caused by solid tumors or lymphoproliferative malignancies such as lymphomas, hairy cell leukemia and chronic lymphocytic leukemia (7). National Comprehensive Cancer Network (NCCN) guidelines have demonstrated that certain types of cancers are associated with an accompanying high risk of developing neutropenia in cancer patients, for instance, cancer of the breast (12).

Cancer treatment modalities also partly contribute to development of neutropenia. Radiotherapy, for instance, when administered to the site of active bone marrow proliferation can predispose patients to developing neutropenia (7). In addition, studies have demonstrated that cytotoxic antimetabolites cause neutropenia through their mode of action (13).

1.4 Management of neutropenia

A risk-index scoring system has been developed by the Multinational Association of Supportive Care of Cancer (MASCC) to assess cancer patients who are at risk of developing chemotherapy-induced neutropenia (14). According to the risk-index scoring system of MASCC, the maximum theoretical score is 26. A patient with a risk-index score of less than 21 is at high risk while ≥ 21 is considered to have a low probability for developing neutropenia (14).

In order to avert the development of neutropenia, international and national guidelines recommend that granulocyte colony-stimulating factor (GCSF) should be used prophylactically among patients receiving cytotoxic chemotherapy with a $\geq$20% likelihood of developing neutropenia. Additionally, cancer patients who have co-morbidities for instance cardiovascular diseases are eligible to receive GCSF prophylaxis even though their risk for developing neutropenia is less than 20% (15). Other treatment modalities of neutropenia include empiric antimicrobial therapy providing broad coverage for both gram negative and gram positive bacteria, antifungals and antivirals.

Adequate management of neutropenia is crucial to the successful achievement of therapy. It may be affected by adherence to treatment which is a multifactorial approach influenced by socio-economic, as well as treatment, health care system, disease and patient-related factors that need

to be addressed (16). In resource-constrained settings such as Kenya, there are limited published literature examining the appropriateness of the utilization of GCSF, factors impacting on neutropenia development and its management. The only available studies pertain to the prevalence of neutropenia and management of neutropenia without providing an insight on knowing whether oncology physicians are prescribing GCSF in accordance with the current guidelines and whether patient profiles play a role.

1.5 Problem statement

The treatments of cancers have over the years focused on the reduction of the tumor burden and prevention of the metastasis of the cancer. This approach has largely ignored the other effects of cancer treatments and led to the development of adverse effects such as neutropenia.

Studies have shown that development of neutropenia is associated with certain types of cancers and cytotoxic chemotherapy regimens (13). There is scant literature on the profiles of patients who develop neutropenia. Furthermore, neutropenia is one of the principal dose-limiting factors for cytotoxic chemotherapy. It can lead to the postponement of anticancer administration to allow the immune system to recover and dose adjustments are required which may necessitate the need to change the cytotoxic chemotherapy regimen (7).

Neutropenia is considered to be an oncologic emergency and requires appropriate management (17) depending on the severity status. If not managed well, neutropenia can cause complications such as fever, bacteremia, superficial and deep tissue infections with bacteria, fungi and viruses, septic shock and eventually death (18).

Neutropenia is managed using GCSF at the primary point of care (13) whose risk assessment is not routinely done in resource-limited settings. The management patterns using GCSF are yet to be characterized in resource limited settings. As GCSF is a drug that requires handling with care including preservation in a cold chain system, there are limited studies to find out how patients store the drug prior to administration. This will ultimately affect its effectiveness and lead to prolonged episodes of neutropenia even after administration.

1.6 Research questions

1. What are the profiles of patients receiving GCSF for the management of neutropenia at Kenyatta National Hospital (KNH)?
2. What is the level of severity of neutropenia and its associated factors among adult cancer patients receiving GCSF at KNH?
3. What are the management patterns of neutropenia using GCSF among adult cancer patients at KNH?
4. What is the source of funding and handling patterns of GCSF prior to administration among adult cancer patients at KNH?

1.7 Objectives

1.7.1 Main objective

To characterize the profiles and management of neutropenia with GCSF among adult patients receiving cancer chemotherapy at KNH

1.7.2 Specific objectives

1. To characterize the profiles of patients receiving GCSF for the management of neutropenia at KNH
2. To establish the level of severity of neutropenia and its associated factors among adult cancer patients receiving GCSF at KNH
3. To describe the management patterns of neutropenia using GCSF among adult cancer patients at KNH
4. To describe the source of funding and handling patterns of GCSF prior to administration among adult cancer patients at KNH

1.8 Study justification

There has been relative little interest in the management of adverse effects that are associated with the use of cytotoxic chemotherapy in the management of various types of cancers. Effective management of the adverse effects associated with the utilization of cytotoxic chemotherapy is one of the key aspects in patient healthcare. This necessitates the need to carry out more studies in order to report the profiles of patients that develop neutropenia in the general adult cancer population in order to guide future management. Locally, one study has documented the risk

factor identification and incidence of chemotherapy-induced neutropenia among patients with cancer at KNH (19), without focusing on other characteristics of patients. GCSF is administered to correct neutropenia in cancer patients. Anecdotal data suggests that not every patient with neutropenia receiving cytotoxic chemotherapy needs GCSF suggesting that the risk assessment is important to determine the severity of neutropenia. It is therefore important to know whether the patients fall into high risk, low risk or intermediate risk for developing neutropenia in order to prescribe GCSF in accordance with established guidelines as well as save on unnecessary costs. Furthermore, it is necessary to characterize patient profiles that have been associated with neutropenia development locally because studies carried out in the West have already demonstrated that certain types of cancers and chemotherapies have an impact. This demonstrates a gap in establishing the need to have local data on the patients' profiles and management of neutropenia among adult cancer patients receiving cancer chemotherapy.

This study makes recommendations to suit the characteristics of adult cancer patients that visit KNH. Profiles such as the high risk cancer chemotherapy regimens that cause neutropenia will aid in providing evidence for the prophylactic utilization of GCSF among adult patients.

To the best of our knowledge, no studies had been done locally to establish patient profiles or discussed the source of funding and handling of GCSF which may impact on the management. This study was a pointer to further guide future management of neutropenia with GCSF as well as the handling processes.

1.9 Conceptual framework

The conceptual framework is demonstrated in Figure 1.

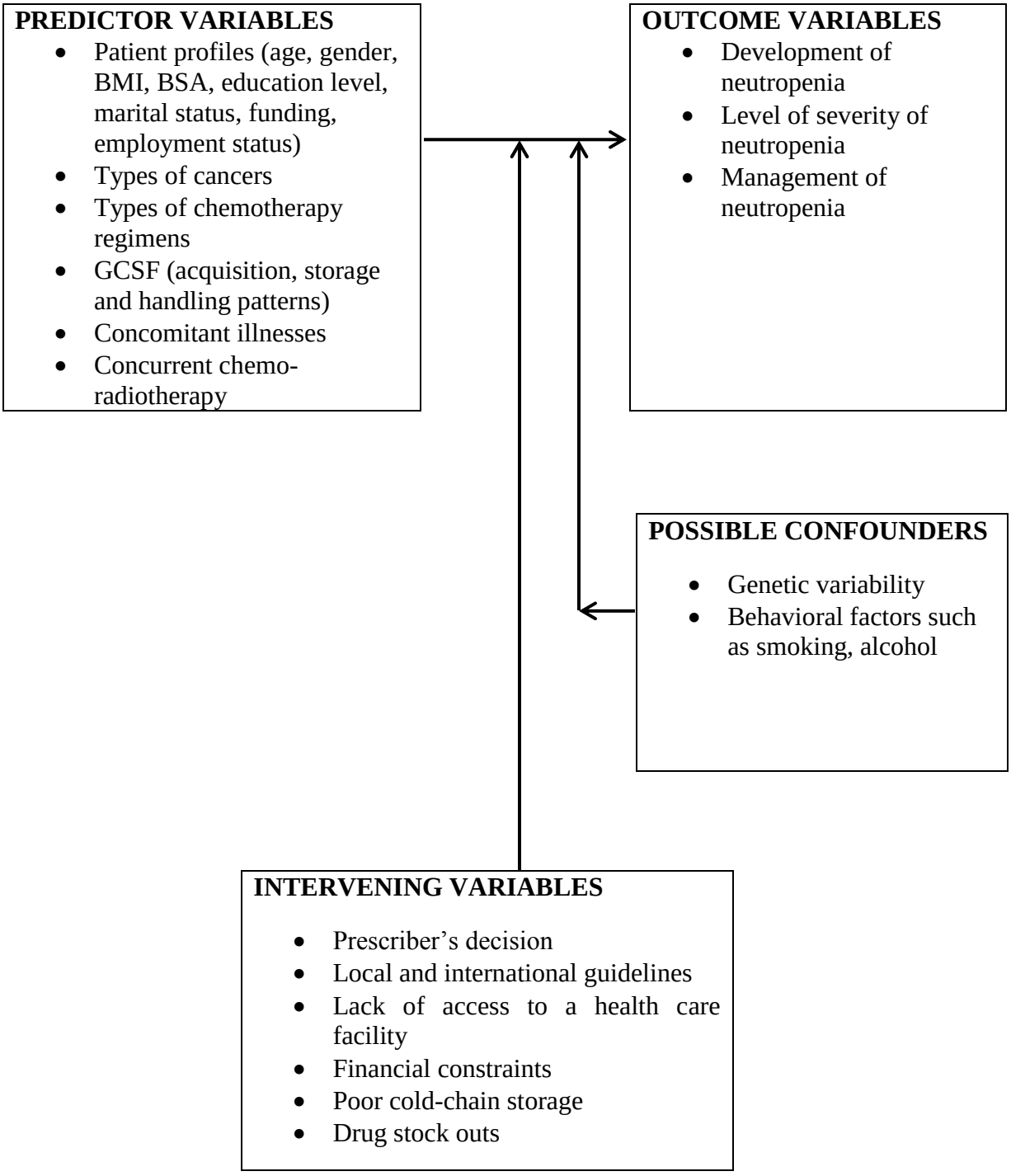

Figure 1: Conceptual Framework

The conceptual framework demonstrates the interaction between both the predictor variables and outcome variables. The endpoint of interest is the development, level of severity and management of neutropenia. The profiles of patients with regards to their source of funding treatment, for instance, can influence their financial capabilities which will ultimately affect the management of the neutropenia which is the outcome of interest. The intervening variables such as the prescriber's decision on whether to use GCSF pre or post-administration of chemotherapy is likely to influence the subsequent level of severity and management of neutropenia. Possible confounders include genetic variability and behavioral factors, such as the smoking and alcohol consumption, need to be controlled for.

1.10 Delimitations

This study only included patients who attended the oncology department at KNH. As a result, the results may not be generalizable to other oncology departments in the country.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

This chapter is designed to describe in detail available literature on neutropenia among cancer patients. It provides an insight on neutropenia including the definition, severity, classification, risk factors and the management. It also describes which cancers and chemotherapy regimens are highly associated with neutropenia development. International guidelines, such as the NCCN, American and European guidelines, have also been reviewed to demonstrate an understanding of how neutropenia among cancer patients is being managed globally.

2.2 Importance of neutrophils and neutropenia

Neutrophils, similarly known as polymorphonuclear leukocytes, are usually produced in the bone marrow. Approximately, 10^{11} neutrophils are synthesized per day. They are the most important effector cells of the immune system's innate arm. They are under constant patrol for the signs of microbial infections and are the first line of the body's defense. There are 3 main antimicrobial functions of neutrophils which include degranulation, expulsion of their nuclear material and phagocytosis (20).

Neutropenia is a decline in the neutrophil count of less than 1.5cells$\times 10^9$/L of blood. The normal lower limit of the neutrophil count is 1500 cells/microliter in the white population and is slightly lower in the black population to about 1200 cells/microliter. The neutrophil counts are usually not stable and can vary over short durations due to factors such as stress, anxiety, exercise and drugs. When making an appropriate diagnosis, several measurements may be needed when classifying the severity of the neutropenia (6).

The absolute neutrophil count is an indicator for the presence of infections, inflammation and other conditions. It is a measurement in blood of the total number of neutrophils. A low absolute neutrophil count indicates that a patient is more susceptible to infections (21). The absolute neutrophil count is calculated as shown below (6).

$$\textbf{Absolute neutrophil count} = \frac{(\%\textbf{neutrophils} + \%\textbf{bands})}{100} \times \textbf{WBCs}$$

2.2.1 Severity of neutropenia

The neutropenia severity is related to the relative likelihood of infection development and is described as shown in Table 1.

Table 1: Severity of Neutropenia (22)

Severity	**Absolute Neutrophil count (cells/µL)**	**Comments**
Mild	1000-1500	It does not impair the host defense, but may necessitate investigation of the underlying cause
Moderate	500-1000	Slightly increases the probability of infection only if other aspects of the body's immune system are impaired
Severe	<500	200-500 /µL has an increased risk of infections
Agranulocytosis	<200	Likelihood of severe, life-threatening infections especially with opportunistic organisms

2.2.2 Classification of neutropenia

Classification of neutropenia is into either primary or secondary as demonstrated in Table 2.

Table 2: Classification of neutropenia (23)

Classification	Cause
Primary neutropenia	Aplastic anemia
	Chronic idiopathic neutropenia
	Cyclic neutropenia
	Myelodysplasia
	Paroxysmal nocturnal hemoglobinuria
	Kostmann syndrome
	Syndrome-associated neutropenias such as dyskeratosis congenital, glycogen storage disease type IB, Shwachmann-Diamond-Oski syndrome, Chediak-Higashi syndrome
Secondary neutropenia	Use of alcohol
	Autoimmune neutropenia
	Bone marrow replacement
	Cytotoxic chemotherapy
	Drug-induced neutropenia such as sulfonamides, penicillins
	Vitamin deficiencies such as folate deficiency, vitamin B12 deficiency, undernutrition
	Hypersplenism
	Infections such as malaria, tuberculosis, brucellosis

Neutropenia is more likely to be secondary rather than primary. Primary neutropenia is usually congenital and not associated with other pathologies (24). From the secondary causes, cytotoxic chemotherapy or radiotherapy for malignant diseases is the most common cause. Drugs cause neutropenia either by direct bone marrow suppression, for example by the use of chloramphenicol, or by immune destruction of the neutrophil or myeloid progenitor cells as it seems with the use of cephalosporins. Drug-induced or immunologically mediated neutropenia is more likely to be underdiagnosed because anti-neutrophil antibodies are not available (25).

2.2.3 Clinical manifestations of neutropenia

When history of patients with neutropenia is taken, the patients commonly report a history of recurrent infections, opportunistic infections and the frequent use of antifungals as well as antibiotics. The physical findings include gingivitis, deep abscess, otitis media, meningitis, mucocutaneous candidiasis, fever, cough, malaise, recurrent tonsillitis, splenomegaly, diarrhea, poor wound healing and a sore throat (26).

There are significant complications accompanying neutropenia development among patient with cancer. Fever during neutropenia is a serious consequence and it likely leads to an increase in the probability of mortality. Febrile neutropenia, which arises as a neutropenic complication, is an oncologic emergency. Serious infections with gram-negative bacteria can occur which are considered to be life-threatening. Not only are gram-negative bacterial infections implicated but also infections with gram-positive bacteria, fungi, protozoa and viruses can lead to significant morbidities and even mortality especially in an immunocompromised neutropenic cancer patient. These infections especially with gram-negative bacteria can lead to the development of septic shock and death if the patient is not managed well. In addition, neutropenic colitis, also known as typhilitis, is a serious complication. Patients typically present with fever and abdominal pain which are non-specific signs and symptoms and can easily be missed. Patients who develop typhilitis are usually treated with antibiotics and conservative measures, but if there is a likelihood of the patient developing an ischemic bowel, surgical interventions may be necessary. Typhilitis is more likely to develop among patients who have hematologic malignancies that are associated with prolonged periods of neutropenia (7).

2.2.4 Neutropenia development risk factors

According to NCCN guidelines, the patient-risk factors that are associated with neutropenia development among patients with cancer include prior cancer chemotherapy and radiotherapy, persistent neutropenia, an age >65 years, bone marrow involvement by tumors, recent surgery associated with or without open wounds, hepatic impairment (bilirubin >2mg/dL) and renal dysfunction accompanied by a creatinine clearance of <50ml/min/1.73m^2 (12).

A risk-index scoring system has been developed by the Multinational Association of Supportive Care of Cancer (MASCC) to assess cancer patients who are at risk of developing chemotherapy-

induced neutropenia. The factors and weights that comprise the MASCC scoring system are as demonstrated in Table 3 (14).

Table 3: MASCC Risk-index factors and weights

Factor	Weight
Burden of febrile neutropenia with no or mild symptoms	5
No hypotension (systolic B.P >90mmHg)	5
No chronic obstructive pulmonary disease	4
Solid tumor or hematological malignancy with no previous fungal infection	4
No dehydration requiring parenteral fluids	3
Burden of febrile neutropenia with moderate symptoms	3
Outpatient status	3
Age <60 years	2

The MASCC risk-index scoring system demonstrates that, the maximum theoretical score is 26. A patient scoring ≥ 21 is considered to have a low probability while a score of <21 is a high risk for developing neutropenia (14). The poor predictors of prognosis include hypotension, dehydration, inpatient status, symptoms of febrile neutropenia, previous fungal infection and an age older than 60 years (7).

The NCCN guidelines recommend that risk assessment needs to be evaluated and is related to the treatment regimen, dose of the cancer chemotherapy and the patient-specific risk factors. The risk for neutropenia needs to be established prior to the first and each subsequent cycle of cytotoxic chemotherapy administration. Risk assessment entails details on the type of cancer, cancer chemotherapy regimen (high-dose, standard dose or dose-dense), intention of treatment (curative or palliative), as well as patient-specific risk factors. Patients are classified into three levels of risk for developing neutropenia which include high, low and intermediate based on the chemotherapy regimen. Patients are assigned a high risk group if the patients have a >20% risk of developing neutropenia. Intermediate and low risk groups are assigned if the patients have a 10-20% or <10% risk of developing neutropenia, respectively (12).

2.3 Factors associated with the development of neutropenia

A meta-analysis carried out to determine patient factors that were associated with neutropenia development among cancer patients found that increased age as well as the mere presence of just one co-morbidity led to an increased likelihood of development of neutropenia by approximately two-fifths and one half, respectively (27). Studies have demonstrated that race has been associated with the incidence of neutropenia. It is documented that in White men the absolute neutrophil count is higher than in black men. Similarly, in terms of gender, the incidence of neutropenia is higher in females than in males (13). It has been demonstrated that certain types of hematological cancers that patients present with which include leukemias, lymphomas, myelodysplastic syndrome and myelomas have been linked to the development of neutropenia (13). Autoimmune conditions including rheumatoid arthritis, Sjögren syndrome in addition to systemic lupus erythematosus have also been described to lead to the development of neutropenia among cancer patients (13). Not only is cancer chemotherapy drugs associated with development of neutropenia, as other drugs have been implicated as well. These drugs include allopurinol, anti-thyroid drugs such as carbimazole, diuretics, ticlodipine, chlorpromazine, clozapine, sulfasalazine, cotrimoxazole, valganciclovir and amoxicillin (28). Patients could be using these drugs for the management of their chronic conditions and can be further augmented by the use of cytotoxic chemotherapy. The prevalence of neutropenia has been on the rise among the Middle East population with the consanguinity of marriages highlighted as one of main reason (29).

2.4 Disease settings and cancer chemotherapy regimens associated with neutropenia

According to the NCCN guidelines, some disease settings and the associated cancer chemotherapy regimens are associated with high (>20%), intermediate (10-20%) and low (<10%) risks for neutropenia development (12). In addition, studies have demonstrated that antimetabolites cause bone marrow destruction which leads to neutropenia because of interference with the synthesis of intracellular folic acid, DNA, RNA and proteins (13). The cytotoxic chemotherapy drugs that are highly associated with the development of neutropenia include cisplatin, etoposide, daunorubicin, fluorouracil, actinomycin, cytarabine, busulfan, ifosfamide, methotrexate and asparaginase (13).

2.4.1 Cancer settings and cancer chemotherapy associated with high risk (>20%) of developing neutropenia

Table 4: High risk for developing neutropenia (12)

Disease setting	Cancer chemotherapy regimen
Bladder cancer	Dose-dense methotrexate, doxorubicin, vinblastine and cisplatin
Bone cancer	Vincristine, doxorubin/dactinomycin and ifosfamide Vincristine, doxorubicin/dactinomycin and cyclophosphamide alternating with ifosfamide and etoposide Cisplatin or doxorubicin Cyclophosphamide, vincristine, doxorubicin or dactinomycin Vincristine, ifosfamide, doxorubicin or dactinomycin and etoposide
Breast cancer	Dose-dense doxorubicin, cyclophosphamide followed by dose-dense paclitaxel Docetaxel, doxorubicin and cyclophosphamide Docetaxel and cyclophosphamide Docetaxel, carboplatin and trastuzumab
Colorectal cancer	Fluorouracil, leucovorin, oxaliplatin and irinotecan
Head and neck squamous cell carcinoma	Docetaxel, cisplatin and 5-fluorouracil
Hodgkin lymphoma	Brentuximab vedotin + doxorubicin, vinblastine, dacarbazine Escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone
Kidney cancer	Doxorubicin or gemcitabine
Non-Hodgkin's Lymphomas	Dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin Ifosfamide, carboplatin, etoposide Dose-dense cyclophosphamide, doxorubicin, vincristine, prednisone Mesna, ifosfamide, mitoxantrone, etoposide Dexamethasone, cisplatin, cytarabine Etoposide, methylprednisolone, cisplatin, cytarabine HyperCVAD- Cyclophosphamide, vincristine, doxorubicin, dexamethasone
Melanoma	Dacarbazine-based combination with interleukin-2, interferon alfa (dacarbazine, cisplatin, vinblastine, interleukin-2, interferon alfa)
Multiple myeloma	Dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide with or without bortezomib
Ovarian cancer	Topotecan Docetaxel
Pancreatic cancer	Fluorouracil, leucovorin, irinotecan, oxaliplatin
Soft tissue sarcoma	Mesna, doxorubicin, ifosfamide, dacarbazine Doxorubicin Ifosfamide or doxorubicin
Small cell lung cancer	Topotecan
Testicular cancer	Vinblastine, ifosfamide, cisplatin Etoposide, ifosfamide, cisplatin Paclitaxel, ifosfamide, cisplatin

2.4.2 Cancer settings and cancer chemotherapy associated with intermediate risk (10-20%) of developing neutropenia

Table 5: Intermediate risk for developing neutropenia (12)

Disease setting	Cancer chemotherapy regimen
Occult primary-adenocarcinoma	Gemcitabine or docetaxel
Breast cancer	Docetaxel Doxorubicin, cyclophosphamide plus sequential docetaxel (taxane portion only) Paclitaxel every 21 days
Cancer of the cervix	Cisplatin or topotecan Paclitaxel or cisplatin Topotecan Irinotecan
Colorectal cancer	Fluorouracil, leucovorin, oxaliplatin
Esophageal and gastric cancers	Irinotecan or cisplatin Epirubicin or cisplatin or 5-fluorouracil Epirubicin or cisplatin or capecitabine
Non-Hodgkin's lymphomas	Gemcitabine, dexamethasone, cisplatin/carboplatin Cyclophosphamide, doxorubicin, vincristine, prednisone including regimens with pegylated liposomal doxorubicin Cyclophosphamide, doxorubicin, prednisone plus brentuximab vedotin Bendamustine
Non-small cell lung cancer	Cisplatin or paclitaxel Cisplatin or vinorelbine Cisplatin or docetaxel Cisplatin or etoposide Carboplatin or paclitaxel Docetaxel
Ovarian cancer	Carboplatin or docetaxel
Cancer of the prostate	Cabazitaxel
Small cell lung cancer	Etoposide or carboplatin
Testicular cancer	Bleomycin, etoposide, cisplatin Etoposide or cisplatin
Uterine sarcoma	Docetaxel

2.5 Management of neutropenia

2.5.1 NCCN guidelines 2020

According to these guidelines, the prophylactic use of growth factors leads to a reduction in the incidence, duration and severity associated with neutropenia. It also leads to a decrease in the

rates of infection, neutropenia-associated hospitalization and leads to the improvements in the administration of full doses of cancer chemotherapy in cancer patients. The recommendation is that if the risk of neutropenia is >20% in a patient, the overall cost of medical treatment is significantly reduced with the use of GCSF prophylactically (12).

Filgrastim is the first novel short acting GCSF drug that has been approved since 1991 by the Food and Drug Administration (FDA) for the management of neutropenia. Novel GCSF drugs have been continuously developed globally for management of neutropenia. Long-acting GCSFs are short-acting pegylated forms of GCSFs with a reduced elimination and enhanced serum half-life after subcutaneous injection (30).

The NCCN guidelines recommend GCSF to be used prophylactically if the cancer patient's risk of neutropenia development is >20% (high risk group) (12). Studies have demonstrated that the prophylactic utilization of GCSF is linked to a 46% decline in the likelihood of developing neutropenia (31). In intermediate risk group (10-20%) of patients, it is recommended that the prophylactic use of GCSF be based on the individualized need according to the patient-specific risk factors. Patients who have a greater or equal to one risk factor should be considered for the use of GCSF prophylactically while those with no risk are recommended to be observed. Patients in the low risk group (<10%) are not recommended to use GCSF prophylactically. However, if the cancer patient is receiving cancer chemotherapy with an intent of cure and has risk factors that are patient-specific for developing neutropenia then the utilization GCSF prophylactically is warranted (12).

2.5.2 American Society of Clinical Oncology (ASCO) guidelines

The MASCC risk-index scoring system (Table 3) or the Talcott's rules (Table 6) are recommended to identify patients in terms of their risks and which candidates are eligible for outpatient management (32).

Table 6: Talcott's rules

Group	Characteristic
I	Inpatient
II	Outpatient with an acute morbidity requiring hospitalization
III	Outpatient without co-morbidity but with uncontrollable cancer
IV	Outpatients with cancer controlled and without comorbidity

Group IV is considered the lowest risk

The ASCO guidelines have recommended the use of empiric antimicrobial drug therapy with the first dose administered within the 1st hour of patient presentation following triage. In the accident and emergency department where patients present with neutropenia and whose risk-index have not yet been established are recommended to receive a dose of empiric antimicrobial drug therapy using the intravenous route initially while still undergoing assessment. Antipseudomonal β-lactam agents such as carbapenems are recommended as monotherapy. Aminoglycosides such as gentamicin, fluoroquinolones such as ciprofloxacin or even vancomycin can be included in the drug regimen for the management of arising complications such as pneumonia or even if antimicrobial drug resistance is proven and/or suspected by cultures and sensitivity (32).

2.5.3 European Society of Clinical Oncology (ESCO) guidelines

The ESCO guidelines advocate for the use of the MASCC index and the NCCN guidelines for scoring patients into high, intermediate or low risk. The guidelines have furthermore recommended the utilization of antimicrobial drug therapy for prevention of neutropenia in patients with high chances associated with cytotoxic chemotherapy. Guidelines from the ASCO and the ESCO recommend the utilization of antimicrobial prophylaxis among high risk cancer patients and advocate for the avoidance for chemoprophylaxis using antimicrobials in the prevention of neutropenia among patients with a low probability. Prophylactic administration of GCSF is recommended if the likelihood of developing neutropenia is greater than 20% during all the cycles of cancer chemotherapy (33).

2.6 Dosing and administration of GCSF and GMCSF

Filgrastim and pegfilgrastim are FDA approved for the prophylaxis of neutropenia among cancer patients with solid tumors receiving myelosuppressive chemotherapy. The NCCN guidelines recommend that filgrastim initial doses are administered subcutaneously the following day or up to a maximum of 3-4 days following the cessation of cytotoxic therapy administration. The dose is 5mcg/kg daily up to the time the post-nadir period absolute neutrophil counts recover to near-normal or normal levels as determined by measurements of laboratory neutrophil counts (12).

Pegfilgrastim is a pegylated version of filgrastim which has been designed to have a longer half-life of 32-62 hours (34) and allows for a single dose administration of 6mg to be sufficient. The NCCN guidelines recommend that administration of pegfilgrastim should be the next day after cytotoxic chemotherapy. Pegfilgrastim is not administered on the same day of cytotoxic chemotherapy. The rationale for this is because of the potential of exacerbation of the neutropenia. This is due to the stimulation of hematopoietic progenitor cells during cytotoxic chemotherapy in dividing cells leads to loss of the progenitor cells. There has to be at least 12 days duration between the dose of pegfilgrastim and the administration of the next cycle of cancer chemotherapy. If the cytotoxic chemotherapy cycle includes the administration of cytotoxics on days 1 and 15, pegfilgrastim can be administered following each chemotherapy treatment (12). GCSF is administered until the neutrophil count is more than 1000 neutrophil/μL for neutropenia (35).

A double-blinded, randomized, clinical trial among cancer patients was carried out to determine the efficacy of filgrastim versus a placebo in increasing the neutrophil counts. An increase in the neutrophil count numbers is seen in 1 to 2 days after starting of therapy. The duration of filgrastim therapy needed to resolve the chemotherapy-induced neutropenia is dependent on the cytotoxic chemotherapy (36).

There are some reported hazards associated with the utilization of GCSF that can limit their use. Bone pain has reported an incidence of 1-5% of all cases; however, not all cases are reported leading to an underestimation of the true incidence in practice. Some of the reported bone pains are associated to be non-responsive to management using non-steroidal anti-inflammatory drugs (NSAIDs) (37). Splenic rupture has also been rarely reported with the use of GCSF. The exact mechanism is not known but it is thought to occur due to the intrasplenic accumulation of

substances such as the circulating granulocytes as well as myeloid precursors. Other toxicities reported include allergic reactions involving the cardio-vascular system, respiratory tract or skin. Other potential toxicities include alveolar hemorrhage, hemoptysis, acute respiratory distress syndrome, sickle cell crisis, mild myalgias, low-grade fever, headache, facial flushing, nausea and dyspnea (12).

GMCSF is also used to promote or accelerate the production of antigen presenting cells or granulocytes. It is approved by FDA to accelerate the myeloid progenitor cells recovery in cancer patients with lymphomas of the Non-Hodgkin's and Hodgkin's type and acute lymphoblastic leukemia in patients who are undergoing transplantation of the stem cell. It is also used in the induction phase of cytotoxic chemotherapy to reduce the duration for neutrophil cell recovery as well as the incidence for the development life-threatening and debilitating infections especially with opportunistic organisms. Globally, the forms of GMCSF available include Molgramostim and sargramostim. Sagramostim is administered at a dose of 250mcg/m^2/day either subcutaneously or intravenously though trials have demonstrated a greater decrease in the duration of neutropenia while using the subcutaneous route of administration. Bone pain and transient fever are more commonly observed in patients receiving GMCSF (35).

2.7 Gaps identified in literature

Publications on the management of neutropenia are available from the Western countries. However, no studies have been done in Kenya to characterize the profiles and management of neutropenia using GCSF among adult patients with cancer. Inappropriate management of neutropenia among cancer patients can lead to febrile neutropenia development as a complication which is considered to be an oncologic emergency (7). This can significantly lead to increased morbidity and mortality among these patients. Upon conducting this literature review, it has been revealed that local and international guidelines that describe the appropriate management of chemotherapy-induced neutropenia among patients with cancer exist. However, evidence is lacking on whether these guidelines have actually been put into practice. Furthermore, Kenyan studies have not revealed what are the profiles associated with neutropenia development amongst cancer patients. Therefore, this study comes a time where this gap indeed needs to be filled. This study provides an insight on the patients' profiles including the types of cancers and cancer

chemotherapy regimens that have been linked to the development of neutropenia. This can aid in generating data on the East African cancer population that will facilitate further research.

CHAPTER 3: METHODOLOGY

3.1 Context of research methodology

This chapter describes in detail how the objectives outlined for this study were achieved. It describes the research design, where the study was conducted, sampling and the target population with a detailed description on the eligibility criteria for participants. The chapter describes the data collection tools that were used, ethical consideration and how the data collected was analyzed for statistical and clinical significance.

3.2 Study design

The research used a cross-sectional study design to characterize the profiles and assess the management of neutropenia among adult patients receiving cancer chemotherapy at KNH. This study design was chosen because it appropriately enabled the achievement of the objectives of this study. This design also aided in examining the relationship between independent and dependent variables of interest as they exist in the target population.

3.3 Study area and site

The study was carried out at KNH, located in Upper Hill, Nairobi, Kenya. It was chosen as the study area as it is the largest national teaching and referral hospital with a bed capacity of 2000. It also provides an excellent medical research environment as it is one of best facilities providing advanced comprehensive cancer treatment in the Eastern and Central region of Africa. It has a high demand for its therapeutic services. The site was the Oncology Department of KNH. It provides chemotherapy, surgical and radiotherapy services for cancer patients. The site was ideal as it easily enabled the required sample size to be achieved. KNH operates an outpatient chemotherapy service run by the cancer treatment center on a daily basis. Chemotherapy is administered to about 220 patients per week on an outpatient basis. The clinic is run by the hemato-oncology unit, department of medicine, every Tuesdays and Wednesdays.

3.4 Target population

The target population consisted of adult cancer patients who developed neutropenia. The eligibility criteria was used to acquire the study population that comprised of adult cancer patients attending the KNH oncology outpatient department who developed neutropenia during

the study period from February 2021 to April 2021 from which the desired sample size was drawn.

3.5 Eligibility criteria

The following sections on the inclusion and exclusion criteria were used to generate the eligibility criteria. The process of eligibility criteria is outlined in Appendix 1.

3.5.1 Inclusion criteria

The inclusion criteria for this study was:

1. Adult outpatient cancer patients.
2. Patients on cytotoxic cancer chemotherapy.
3. Patients who attended the hemato-oncology unit clinic.
4. Adult cancer patients with neutropenia confirmed by the availability of recent complete blood counts.

3.5.2 Exclusion criteria

The exclusion criteria for this study were:

1. Patients with renal and liver impairment as they may interfere with the results of the study because they are known to cause neutropenia.
2. Patients who were on chemotherapy but they were not visiting the oncology department.

3.6 Sample size estimation

The primary endpoint of the present study was the development of neutropenia among the target population. A study carried out by Kawinzi et al at Moi Teaching and Referral Hospital in 2015, documented a prevalence of 10.5% of chemotherapy induced neutropenia (11). Therefore, using this prevalence rate, the sample size was estimated by Cochran formula (38) which had been applied for such epidemiological surveys.

The following formula by Cochran (38) was used:

$$n = \frac{pqz^2}{e^2} \quad \text{.....Equation 1}$$

Where:

n is the desired sample size

p is the prevalence of neutropenia from previous studies

q is the accepted level of precision that is 1-p

z is the standard deviation for a 95% confidence interval which is 1.96

e is the acceptable margin of error that is 5%

Computing these values yielded the following sample size for the study:

$$n = \frac{0.105 \times (1-0.105) \times 1.96^2}{0.05^2}$$

$$n = 144$$

This sample size was adjusted upwards by 5% to cater for non-responders and attrition to get:

$$n = \frac{105 \times 144}{100}$$

$$n = 151$$

Therefore, 151 eligible participants were studied

3.7 Participant selection

A total of 179 participants were initially selected for the study but 151 were included and the reasons for exclusion of 28 patients are presented in the consort diagram in Figure 2.

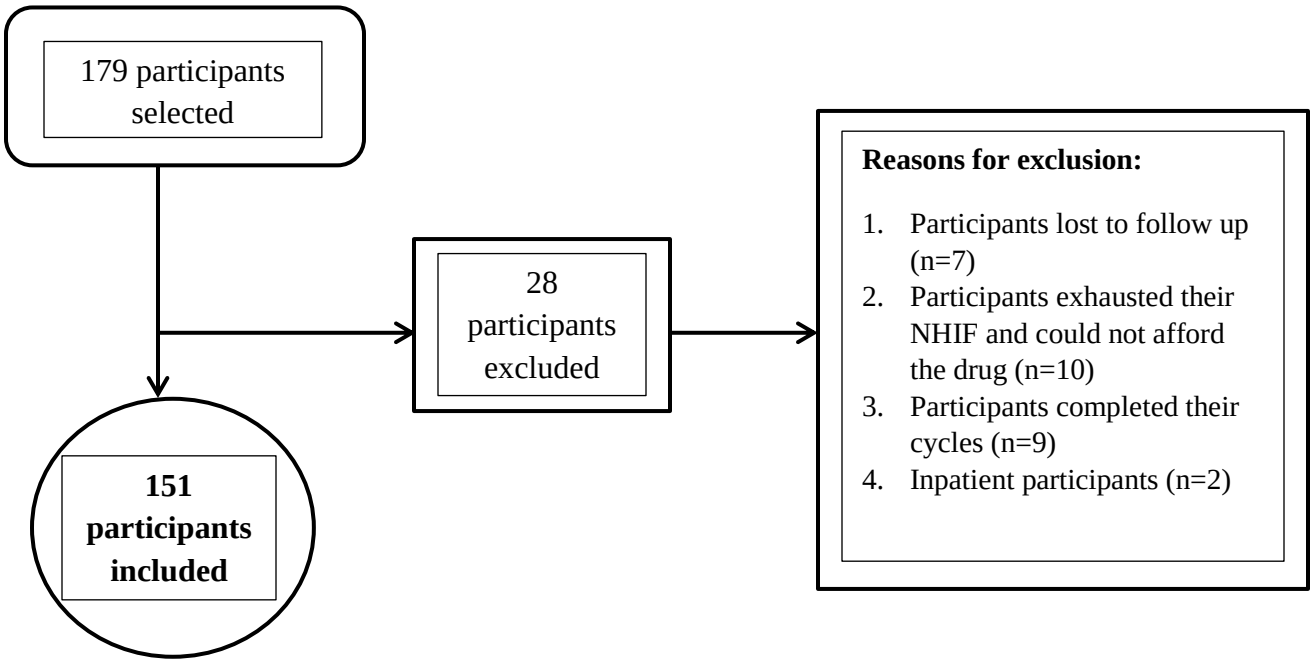

Figure 2: Consort diagram for recruitment of participants

3.8 Sampling method

Consecutive sampling method was employed to achieve the desired sample size. The principal investigator perused through the patients files to identify those with documented neutropenia and also satisfied the eligibility criteria. From these patients, a representative sample was drawn randomly using consecutive sampling. All the eligible files were tagged so that the patients were not lost. Therefore, only patients who developed neutropenia were identified and given a unique identifier code generated by the principal investigator for purposes of data collection.

3.9 Participants recruitment and consenting process

A predesigned data collection form was used to extract the raw data. Cancer patients usually attend the cancer treatment center for management. Initially, the cancer patients were seen by the nurse for triage where their temperature and blood pressure were recorded. The cancer patients then proceeded to be reviewed by the oncologist. The patient was reviewed, the chemotherapy regimen checked and the necessary laboratory measurements done while ensuring that complete blood work were done. Blood counts and renal function tests were carried out and then the patients and their files were sent to the pharmacist. If the oncologist diagnosed neutropenia at his point of patient contact, then a prescription of GCSF was prepared.

At the pharmacy, the pharmacist had to review the file to check the regimen, chemotherapy cycle and blood parameters of the patients. GCSF was then dispensed and administered. If the pharmacist discovered any discrepancies with regards to the absolute neutrophil counts, he/she went back to the oncologist and they discussed the patient. They all agreed to either proceed with the administration of cytotoxic chemotherapy and those who had neutropenia were sent back to the pharmacy and nursing unit for the administration of GCSF. These patients deferred chemotherapy until the neutrophil counts had risen to appreciable levels.

At the point of dispensing, the staff had to enquire if the patient was paying via cash, NHIF or private insurance. If the mode of payment was cash, the patient cleared the bill and was administered the GCSF on the same day. If NHIF was the mode of payment, then necessary financial documents needed to be processed and sent for approval from the department. The approval process took about 48 hours and therefore in this case, the patient had to wait for 48 hours to get the GCSF. It was advisable to request for both the cytotoxic chemotherapy and GCSF on the same NHIF form rather than using two separate request forms as this would compromise the next cycle coverage for the patient.

Two days after the administration of the GCSF, the patient had to be reviewed again to do a repeat complete blood count to reassess the absolute neutrophil count to determine whether or not to proceed with cancer chemotherapy administration. If the cancer patient was at the borderline of neutropenia (1000cells/µL), then the team decided to proceed with cancer chemotherapy administration followed by GCSF administration 48 hours post-chemotherapy. These cancer patients were then reviewed in their next cancer chemotherapy cycle.

The patients were identified at the pharmacy by the pharmacist using their files and their names were noted only for purposes of invitation to interview them. The patients were then recruited using the eligibility criteria and a consent form was administered to the patients. If the cancer patients gave their consent voluntarily then data was collected from them. The informed consent form delivered is shown in Appendix 3.

3.10 Research instruments and data collection

A data collection tool (Appendix 2) was used to collect the relevant data for the objectives of this study. The tool was designed to capture details of the patient demographics (age, gender, body

surface area, area of residence, occupation, level of education, employment, social support, mode of funding treatment, marital status, tobacco smoking and alcohol consumption). History of the presenting cancer and cancer chemotherapy regimen details were also captured (type, stage, concomitant illnesses, chemotherapy regimen and radiotherapy). The severity of neutropenia was captured. The tool was also designed to record data from the point of the oncologists to determine whether they were prescribing GCSF in tandem with the current guidelines. This information was captured based on what intervention the prescriber indicated in the patient's file. The effectiveness of GCSF was captured by this tool as it recorded the absolute neutrophil counts prior to and after GCSF administration. The dose and duration of use, storage conditions from the patient's point (refrigeration or cool box provisions), cost and method of acquisition of GCSF were also captured.

3.11 Medical record and medication chart review

The data collection was done at the point of the pharmacy. The patient file provided details such as the name, age, body surface area (weight, height), cancer type, cancer chemotherapy regimen, the number of cycles, physician's intervention against the neutropenia and the laboratory measurements. Using the data collection tool, the data collector interviewed the patients receiving NHIF on determining where they stayed when they were awaiting approval and if they had the necessary storage equipment to store the drug in case they needed to take it home. Any information that was not provided by the patient during the interview was extracted from the patients' file; for instance the patients did not know the dose of GCSF they were being administered and using the patients' file, the principal investigator was able to extract this information. Similarly, some patients did not know what they had been prescribed for the management of their neutropenia, and then the patients' files became useful.

3.12 Piloting of the study

Piloting was done randomly on 16 selected neutropenic patients. This formed the basis for pre-testing of the data collection tool to determine whether the research was realistic and workable. The pilot study was only done after ethical approval had been granted by the Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (KNH/UoN-ERC). The data collected was assessed for whether the tool could adequately collect data that would meet the objectives of the study. The results informed the principal investigator on whether the tool

needed any modifications. If any discrepancies had been noted, the corrected tool would have been modified and submitted again to KNH/UoN-ERC for approval before use. The piloted sample size was, however, not used for data analysis in this study.

3.13 Quality Assurance, Validity and Reliability of the Collected Data

3.13.1 Quality Assurance

The quality of the research was ensured by using a well-designed data collection tool that was approved after review by KNH/UoN-ERC. Standard operating procedures were used for collecting data. Regular meetings were scheduled with the supervisors with regards to the progress of the research and any deviations from protocol were captured early enough. Site pre-assessment was done to confirm the availability of data relevant to the study. A research assistant underwent training by the principal investigator. On-the-spot examination of the research assistant was done by the principal investigator.

3.13.2 Validity

Validity in research is the measure of how well an instrument is designed to test its intended work. It is the truthfulness of the research findings (39). The validity of this study was accomplished by the data collection tool. The pilot study was able to validate whether all relevant information would be captured by the data collection tool. The pilot study addressed any measurement errors that would be generated by either the researcher or the situational factors and thereby reduce the likelihood of generation of bias.

3.13.2.1 External Validity

This enables the findings of the research to be generalized to the entire population. This was achieved by the pilot study in that the target population was clearly defined. The eligibility criteria were assessed for restrictiveness as a very restricted eligibility criterion would minimize generalizability. The sampling method was also assessed as it would affect generalizability.

3.13.2.2 Internal Validity

This provides a direction on how well the study will be done to yield credible results for generalizability. The pilot study assessed how well the data collection tool had been designed. This formed the basis of using a pretested and validated data collection tool.

3.13.3 Reliability

Reliability in research is the measure to which research methods can be repeatedly applied to come up with consistent research findings (40). The pilot study determined whether the tool captured the relevant data with regards to the objectives of the research. This was demonstrated when consistent results were obtained. The reliability of study was assured by the use of trained and qualified staff and verification of the data once it was collected.

3.14 Study Variables

Independent Variables

The independent variables included the patient demographics such as age, gender, weight, height, occupation, area of residence, county, level of education, employment, social support, marital status, tobacco smoking and alcohol consumption. The history of the presenting cancer, staging, comorbidities and cancer chemotherapy treatment modalities also fell in this category of variables.

Dependent Variables

The predictor (independent) variables were the patient profiles while the outcome (dependent) variables were the level of severity of neutropenia and the management outcomes.

3.15 Data Management

3.15.1 Data processing

The data was coded and entered into Microsoft Excel version 2016 to create the database. The unique identifier code was generated by using the following components first letters of the first name and surname, gender (M for male and F for female) and the date or year of birth of the patient. For instance, Anita Babra, female born on 26th July 1993 had the unique identifier code of AB/F/2693. However, upon identifying patients being covered by NHIF, their names were recorded for follow up purposes only to determine when they received the GCSF. The electronic database was password protected and access limited only to the principal investigator. An additional backup was created using an external drive that was stored and backed up regularly in a separate location under lock and key away from the primary data. The hard copies of the

primary data collection tool were kept in a lockable cabinet accessible only to the principal investigator for a period of 2 years after which they will be destroyed.

3.15.2 Data analysis

Data was cleaned and exported to STATA statistical software version 23 for data analysis.

3.15.2.2 Univariate analysis

Analysis of patient socio-demographics was done using univariate analysis. Socio-demographic and clinical characteristic variables such as age, weight, height, gender, occupation, level of education, marital status, tobacco smoking and alcohol consumption patterns were summarized using descriptive statistics where the mean, median, standard deviation, frequencies and percentages were obtained. The univariate data was represented using frequency tables, bar charts and pie charts.

3.15.2.3 Bivariate analysis

Bivariate analysis was conducted to determine associations between the severity of neutropenia and the profiles' of participants (sociodemographic and clinical characteristics). The Chi-square/Fischer's exact test was employed for categorical independent variables and the severity of neutropenia. Student T-test was used to assess the differences between the participants who were neutropenic versus those who did not develop neutropenia in terms of their age, BMI and BSA scores.

3.15.2.4 Multivariable analysis

The results of the bivariate analyses informed the multivariate analysis. Multivariate logistic regression was used to determine independent correlates of the severity of neutropenia. The logistic regression model or the logit model is a special case of a generalized linear analysis model where the outcome is a nominal variable. This technique enables adjusting for many explanatory factors and controlling for confounders as well as enabling easy detection of interactions between explanatory factors. It is flexible, easy to use and usually gives meaningful interpretations by giving the magnitude and the direction of the association between explanatory and outcome variables.

All variables that were associated with the outcome variable at $p \leq 0.05$ were entered in the multivariate logistic regression models to control for confounders and effect modifiers. This helped to identify independent covariates of the severity of neutropenia. A p-value of ≤ 0.05 was

used as the criterion for statistical significance and adjusted odds ratio (AOR) with 95% confidence interval were used to indicate the strength of association.

3.16 Ethical Considerations

3.16.1 Study approvals

Ethical approval was sought from the KNH/UoN-ERC before the study commenced; reference number **P598/10/2020** (Appendix 5). Additional approval was obtained from the KNH Research and Programs department and the oncology department before conducting the study; study registration number **Pharmacy/49/2021** (Appendix 6).

3.16.2 Informed consent

The principal investigator disclosed the entire details of the research to the participants. Any doubts were clarified and patients were assured that no risks would be imposed to them. An approved informed consent form (Appendix 3) from KNH/UoN-ERC was provided to the participants before interviewing them. Only those who voluntarily consented were interviewed and no coercion was done to include any participant.

3.16.3 Confidentiality

Confidentiality of patient data was of utmost concern in this study. There were unique identifier codes generated to hide patient details. Additionally, hard copy records were stored in a lockable cabinet and electronic databases were password protected with access solely limited to the principal investigator. Patient details of whatsoever nature were not revealed to any interested person(s) or party(ies) under any conditions.

3.16.4 Benefits of the study

This study gave an insight on the management of neutropenia using GCSF that is crucial to improve patients' quality of life. The information will be used to promote the management of neutropenia depending on the profiles of patients. From this study, information pertaining to the use of GCSF in neutropenia will be of value to other oncology units in the country, including the researchers.

3.16.5 Risks from the study

This study did not introduce any risks to patients as patient files and interviews were used only to extract information. No medications were administered as this was not an interventional study.

3.17 Dissemination Plan

At the conclusion of the study, the research findings were disseminated to the oncology medical team. A dissertation copy was prepared with the soft copy made available online at the University of Nairobi repository while the hard copy was made available at the University library and the department of Pharmaceutics and Pharmacy Practice. Manuscripts were prepared for dissemination of research findings in scientific journals. Furthermore, during scientific seminars and continuous medical educations (CMEs) presentations were done for further dissemination of research findings. This study was funded by KNH and a copy of the study was presented to the KNH research and programs department for research purposes. A policy brief was prepared and disseminated to the oncology department of KNH through the research and programs department.

3.18 Research funding

The study was financially funded by the 2020/2021 KNH Research Fund (Reference number: **KNH/R&P/23J/98/8**).

CHAPTER 4: RESULTS

4.1 Participants socio-demographic and socio-economic characteristics

The sociodemographic characteristics of the study population are presented in Tables 7 and 8.

Table 7: Participants socio-demographic characteristics

Variable	Category	Frequency (N=151)	Percentage (%)
Gender	Male	43	28.5
	Female	**108**	**71.5**
Age	40 and Below	16	10.6
	41-50 Years	41	27.2
	51-60 Years	41	27.2
	Above 60 Years	**53**	**35.1**
Mean Age	Mean (SD)	54.2	12.3
Age at Diagnosis	40 and Below	24	15.9
	41-50 Years	43	28.5
	51-60 Years	40	26.5
	Above 60 Years	**44**	**29.1**
Mean Age at Diagnosis	Mean (SD)	52.3	12.3
Body Mass Index(BMI)	Underweight (<18)	15	9.9
	Normal (18-25)	**66**	**43.7**
	Overweight (25-30)	38	25.2
	Obese (>30)	32	21.2
Mean BMI	Mean (SD)	25.2	6.1
Body Surface Area (BSA)	Mean (SD)	1.7	0.2
Education Level	No Formal Education	11	7.3
	Primary	42	27.8
	Secondary	**75**	**49.7**
	Tertiary	23	15.2
Religion	**Christians**	**148**	**98.0**
	Non-Christians	3	2.0
Marital Status	**Living With a spouse**	**105**	**69.5**
	Not Living With a spouse	46	30.5
Smoking	**No**	**149**	**98.7**
	Yes	2	1.3
Alcohol Use	**No**	**149**	**98.7**
	Yes	2	1.3
Residence	Rural	60	39.7
	Urban	**91**	**60.3**
Employment Status	Employed	51	33.8
	Unemployed	**100**	**66.2**

The study population comprised mostly of female participants (108, 71.5%). The mean age of the participants was 54.2 years (±12.3) but ranged 16 to 79 years while the mean age at diagnosis of cancer was 52.3 years (±12.3). Majority (75, 49.7%) had secondary level education, were Christians (98%), married (105, 69.5%) and did not smoke or consume alcohol. Sixty percent lived in urban areas and two-thirds were unemployed.

The study population had a mean BMI of 25.2kg/m^2 (± 6.1) with a range of 11.79 to 44.85kg/m^2 (Table 7). Majority of the patients (43.7%) had a normal BMI with a mean BSA of 1.7m^2 (±0.2).

Table 8: Socio-economic characteristics of participants

Variable	Category	Frequency (N=151)	Percentage (%)
Transport to hospital	Private Means	18	11.9
	Public Means	**133**	**88.1**
Residence Awaiting Chemotherapy	**Home**	**82**	**54.3**
	Away from Home	69	45.7
Social support family	No	18	11.9
	Yes	**133**	**88.1**
Social Support friends	**No**	**135**	**89.4**
	Yes	16	10.6
Social Support charitable organization	**No**	**147**	**97.4**
	Yes	4	2.6
Funding	**NHIF**	**117**	**77.5**
	Cash and others	34	22.5

Key: NHIF – National Health Insurance Fund

Approximately half (54.3%) of the participants reported that they would come from home on a daily basis to receive their treatment using mainly public transport (88.1%). Majority of participants (133, 88.1%) reported that they were socially supported by their families during their course of the management of their cancer. Three-quarters of the study population were funded by NHIF for their cancer management (Table 8). Several participants had depleted their cycles of use of NHIF and had to wait for renewal in the next financial year.

4.2 Counties of participants

Appendix 4 summarizes the counties from where participants came for their cancer treatment. Participants from Nairobi county accounted for the highest number (30, 19.9%) of attendance closely followed by Kiambu county (26, 17.2%).

4.3 Types of cancer among participants

The types of cancer that were associated with the development of neutropenia among the study participants are illustrated in Figure 3.

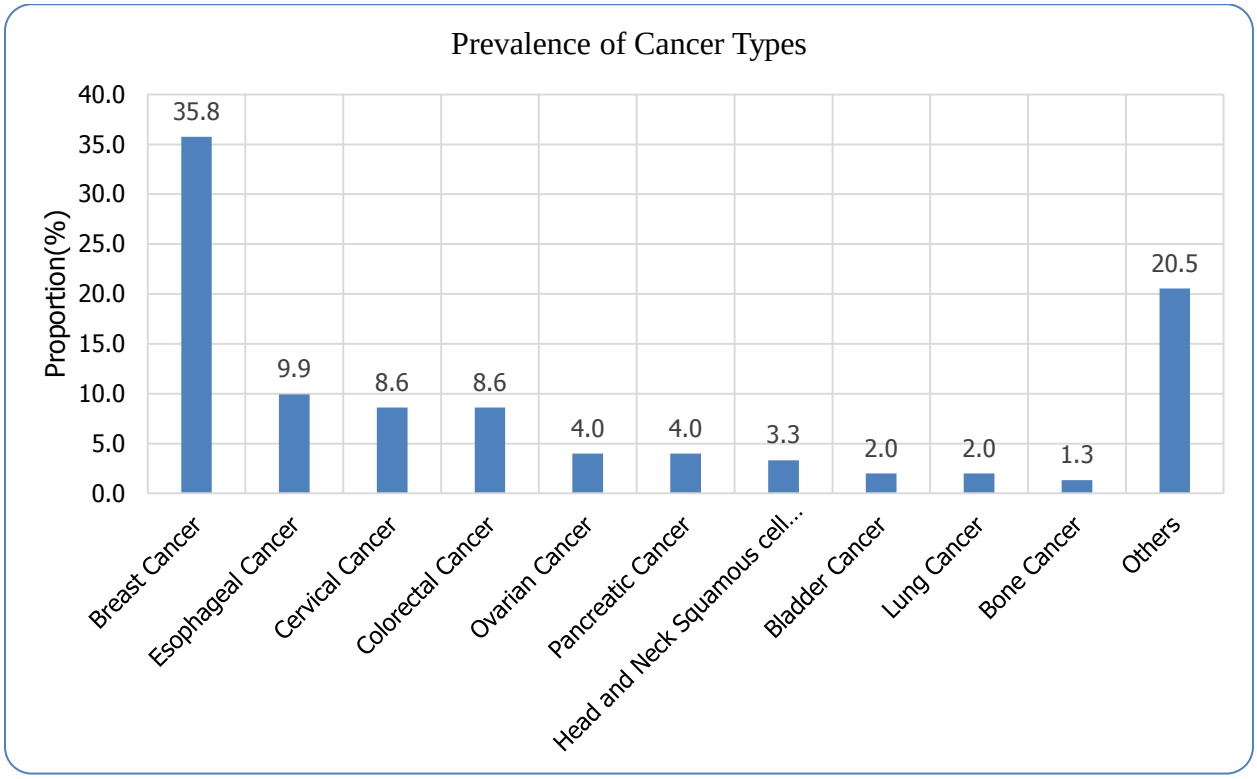

Figure 3: Prevalence of the types of cancer

Others include: Chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma, fibrosarcoma, gastric cancer, Kaposi's sarcoma, plasma blastic lymphoma, cholangiocarcinoma, acute lymphoblastic leukemia (ALL), synovial cancer

The most common types of cancer associated with the development of neutropenia were breast cancer (35.8%), esophageal cancer (9.9%) closely followed by colorectal and cervical cancer (8.6%). Breast, esophageal, colorectal and cervical cancers significantly contributed to 62.9% of the total types of cancer (Figure 3).

4.4 Stages of cancer among participants

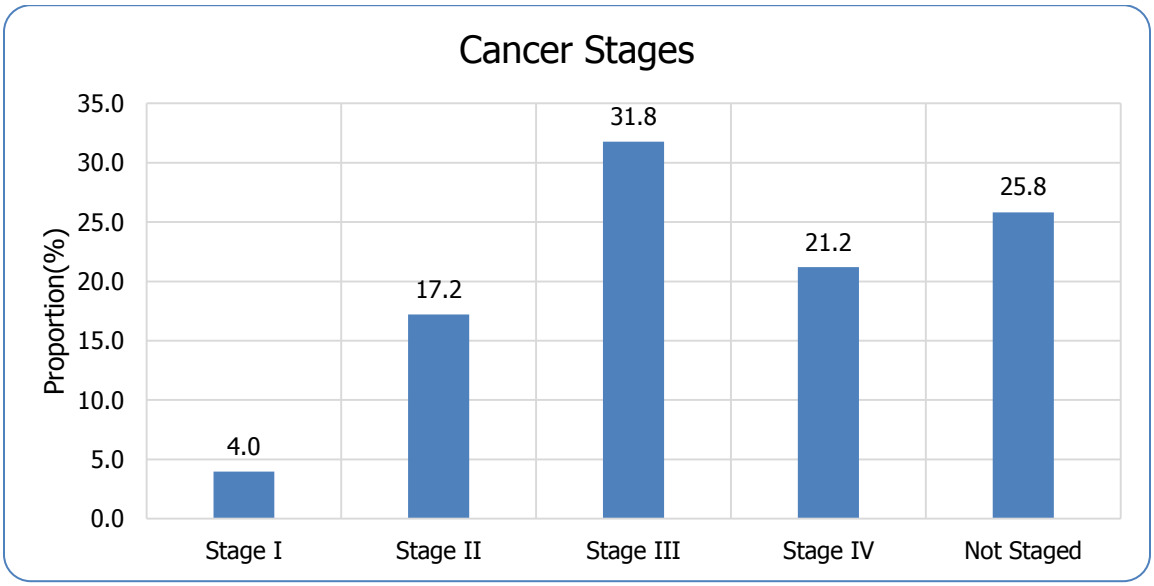

Figure 4: Cancer stages among participants

Approximately a third of the participants were in stage III of their cancer. Participants who are not staged accounted for 25.8% as demonstrated by Figure 4.

4.5 Concomitant illnesses among cancer participants

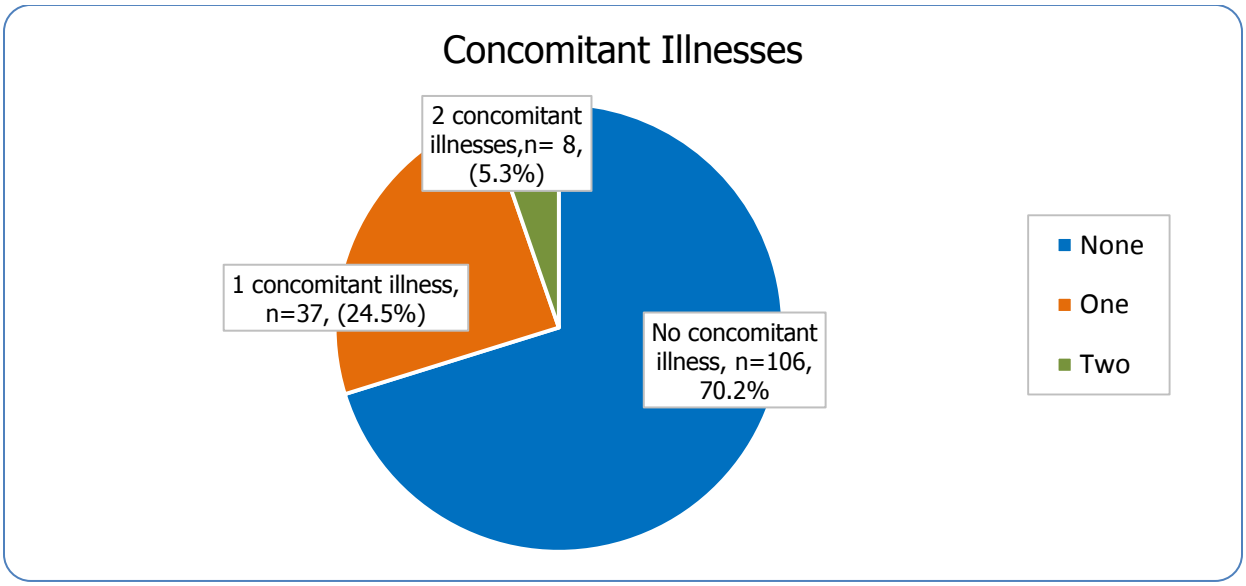

Figure 5: Concomitant illnesses among participants

Thirty seven (24.5%) of the participants had one concomitant illness while 8 (5.3%) had two concomitant illnesses. The rest of the participants did not have any concomitant illnesses.

Prevalence of comorbid illnesses among the participants are summarized in Figure 6.

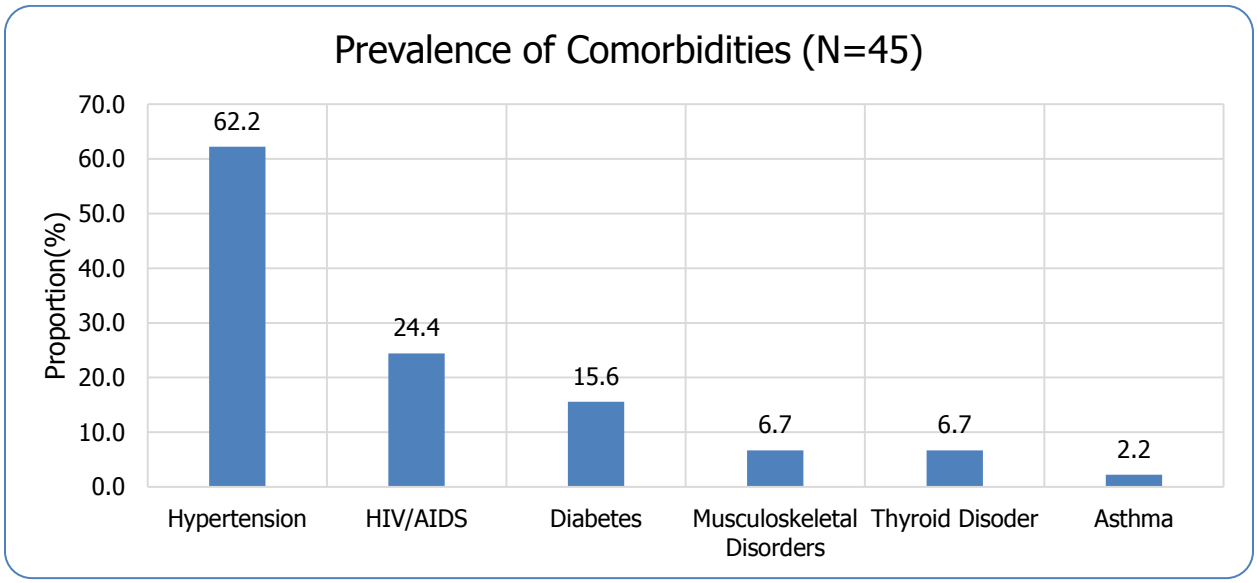

Figure 6: Prevalence of comorbidities among participants

Hypertension (62.2%), HIV/AIDS (24.4%) and diabetes (15.6%) accounted for the most common comorbid illnesses among the study participants. The mean duration of sickness with hypertension among the participants was 75.3 months, HIV/AIDS, 82 months and diabetes, 65.7 months.

4.6 Cancer chemotherapy regimens

Dual therapy accounted for 82.1% among the participants. Mono and quadruple therapies accounted for 17.9% as illustrated in Figure 7.

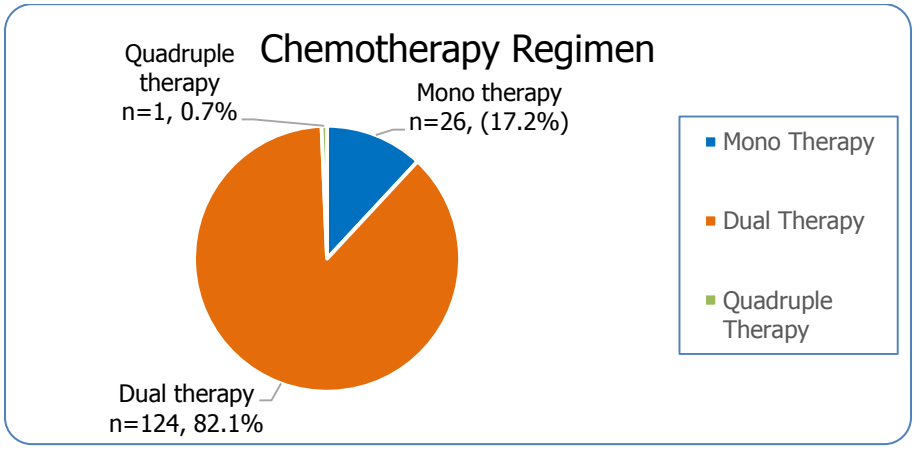

Figure 7: Cancer chemotherapy regimens

Table 9 shows the cancer chemotherapy regimen combinations used by the study participants.

Table 9: Cancer chemotherapy regimen combinations

Chemotherapy Regimen	**Frequency (N=151)**	**Percentage (%)**
Cisplatin-based regimens	33	21.9
Cisplastin Alone	12	7.9
Cisplastin+ Gemcitabine	11	7.3
Cisplastin +Paclitaxel	10	6.6
Carboplatin-based regimens	41	27.2
Carboplatin Alone	1	0.7
Carboplatin +Paclitaxel	28	18.5
Carboplatin + Gemcitabine	11	7.3
Cyclophosphamide-based regimens	38	25.2
Cyclophosphamide + Doxorubicin	37	24.5
Cyclophosphamide + Doxorubicin+ Vincristine + Rituximab	1	0.7
Oxaliplatin-based regimens	21	13.9
Oxaliplatin +Capecitabine	20	13.2
Oxaliplatin + Gemcitabine	1	0.7
Paclitaxel Alone	6	4.0
Trastuzumab Alone	4	2.6
Gemcitabine-based regimens	4	2.6
Gemcitabine Alone	1	0.7
Gemcitabine + Capecitabine	1	0.7
Docetaxel + Gemcitabine	2	1.3
Others	5	3.3

Others include: Palbociclib + Anastrazole, Vinorelbine, Docetaxel, Bendamustine + Rituximab, Trastuzumab + Capecitabine

Carboplatin-based regimens (27.2%) were the most commonly encountered regimens closely followed by cyclophosphamide-based regimens (25.2%). Additionally, the most commonly used

combination regimen was that of Cyclophosphamide and Doxorubicin (24.5%), followed by Carboplatin and Paclitaxel (18.5%) as illustrated in Table 9.

At the time of study, participants were at various stages/cycles of chemotherapy administration ranging from 1-9. Majority of patients were scheduled for six cycles (68.9%) and four cycles (18.5%) of chemotherapy administration regimen. Furthermore, 41 (27.2%) of the participants were in their fourth cycle of chemotherapy administration while 33 (21.9%) were in their second cycle at the time of study as shown Figure 8.

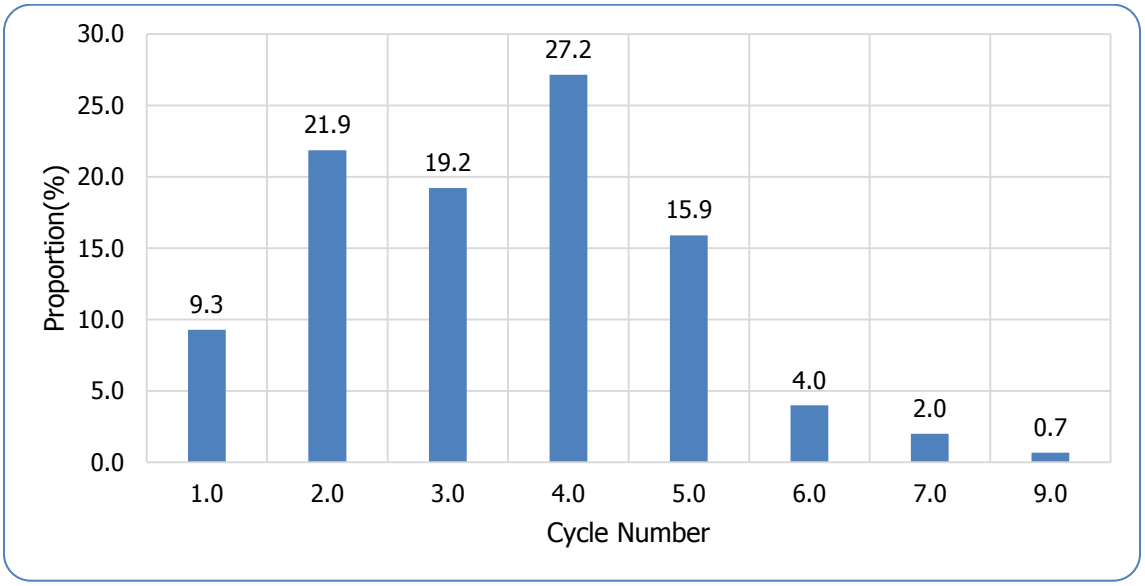

Figure 8: Participants cycle number

4.7 Radiotherapy administration

Only 11.9% of the participants were receiving concurrent radiotherapy with their cancer chemotherapy of which, 13 (72.2%) had received >25 sessions of radiotherapy while 5 (27.8%) had been given <25 sessions. The most commonly radiated site was the pelvic region among the participants who received concurrent radiotherapy.

4.8 Characterization of the neutrophil count levels among the participants

The neutrophil counts were grouped based on the severity of neutropenia. Table 10 shows the severity of neutropenia at pre and post GCSF administration among the participants.

Table 10: Severity of neutropenia before and after GCSF administration

Neutrophil counts	Severity	Pre-GCSF	Post-GCSF
≥2.0× 10^9/L	Normal	1(0.7%)	102(67.5%)
1.0-1.9 × 10^9/L	Mild	83(55.0%)	38(25.2%)
0.5- <1.0 × 10^9/L	Moderate	56(37.1%)	10(6.6%)
0.2- <0.5 ×10^9/L	Severe	10(6.6%)	1(0.7%)
<0.2 ×10^9/L	Very severe/Agranulocytosis	1(0.7%)	0(0.0%)

Before GCSF administration, 83 (55.0%) and 56 (37.1%) of the participants had mild and moderate neutropenia, respectively. After administration of GCSF, approximately two thirds (67.5%) of the participants had normal neutrophil counts while a quarter still presented with mild neutropenia (Table 10).

The median neutrophil count before GCSF administration was 1.09×10^9/L [0.73] indicating mild neutropenia while the median count after GCSF administration was 2.73×10^9/L [3.44] (p <0.001). Pre-GCSF administration, 84 (55.6%) of the participants had their neutrophil counts above the average value of 1×10^9/L while post-GCSF administration 110 (72.8%) of the participants had below the average value of 4.608×10^9/L.

4.9 MASCC Risk index scoring

The mean MASCC risk score was 20.2 ($\pm$1). Participants at a low probability (score of $\geq$ 21) of developing neutropenia attributed to 61.6% while those at a high probability (score of <19) of developing neutropenia accounted for 38.4%.

4.10 Management of Neutropenia

Figure 9 illustrates the various strategies used to manage neutropenia among the participants.

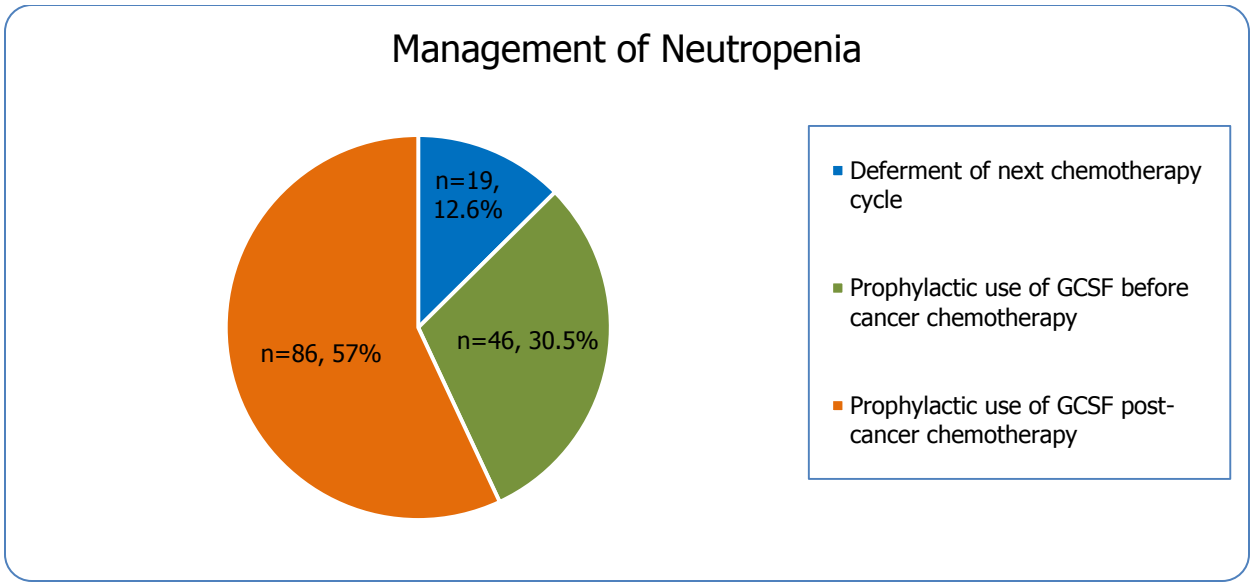

Figure 9: Management of neutropenia

GCSF administration post cancer chemotherapy was the most frequently (57.0%) neutropenia management strategy among participants (Figure 9). The mean dose of GCSF administered across the participants was 5.95 mcg/kg (±2.04) per day. The mean duration of therapy was 3.03 days (±0.29).

GCSF is a temperature sensitive drug requiring storage at 2 to 8 degrees Celsius. Table 11 shows how patients handled GCSF while awaiting administration.

Table 11: Storage and handling of GCSF

Variable	**Category**	**Frequency (N=151)**	**Percentage (%)**
Refrigeration	**No**	**109**	**72.2**
	Yes	42	27.8
Use of Cool Boxes	**No**	**113**	**74.8**
	Yes	38	25.2
Storage at Healthcare	No	22	14.6
Facility Near Home	**Yes**	**129**	**85.4**

One hundred and nine (72.2%) did not store the drug in the refrigerator, while 25.2% and 85.4% stored GCSF in cool boxes and nearest health facilities, respectively.

4.11 Acquisition of GCSF

GCSF is an expensive drug and the mode of acquisition among the patients may impact on its use as well as the management of neutropenia. Table 12 summarizes how the patients acquired GCSF.

Table 12: Acquisition of GCSF

Variable	Category	Frequency (N=151)	Percentage (%)
Receive GCSF Previously	No	24	15.9
	Yes	**127**	**84.1**
Reasons For not Receiving (N=24)	No Knowledge	1	4.2
	Not quoted on NHIF form	1	4.2
	Out of stock	**20**	**83.3**
	Non-Response	2	8.3

Previously prescribed GCSF was administered to majority of participants (84.1%). However, in the remaining (15.9%), GCSF being out of stock was the main reason (83.3%) for failure of administration and this necessitated them to look for it from other facilities including private hospital institutions. During the study period, GCSF was out of stock for a period of 2 weeks.

4.12 Bivariate and Multivariate analysis

Bivariate analysis was carried out to determine the factors associated with the development of neutropenia using the cutoff for neutrophil counts as $\leq 1.5\times10^{9}$/L (neutropenic) as suggested in the literature (6).

4.12.1 Association between patients profiles and development of neutropenia pre-treatment with GCSF

There was no statistically significant relationship between the level of neutrophil count and other sociodemographic factors as displayed in Table 13.

Table 13: Association between profiles of the participants and levels of neutropenia before treatment with GCSF

Variable	Category	Normal ($>1.5\times10^9$/L) (n=42; 28.8%)	Neutropenic ($\leq1.5\times10^9$/L) (n=109; 72.2%)	p-value
Gender	Male	11(25.6%)	32(74.4%)	0.699
	Female	31(28.7%)	77(71.3%)	
Age	50 and Below	15(26.3%)	42(73.7%)	0.749
	Above 50 Years	27(28.7%)	67(71.3%)	
Age at Diagnosis	50 and Below	17(25.4%)	50(74.6%)	0.550
	Above 50 Years	25(29.8%)	59(70.2%)	
BMI	Underweight +Normal	24(29.6%)	57(70.4%)	0.592
	Overweight and obese	18(25.7%)	52(74.3%)	
Education level	Primary and below	12(22.6%)	41(77.4%)	0.299
	Secondary and above	30(30.6%)	68(69.4%)	
Religion	Christians	41(27.7%)	107(72.3%)	0.829
	Non-Christians	1(33.3%)	2(66.7%)	
Marital Status	Living With a spouse	29(27.6%)	76(72.4%)	0.935
	Not Living With a spouse	13(28.3%)	33(71.7%)	
Smoking	No	41(27.5%)	108(72.5%)	0.481
	Yes	1(50.0%)	1(50.0%)	
Alcohol use	No	41(27.5%)	108(72.5%)	0.481
	Yes	1(50.0%)	1(50.0%)	
Residence	Rural	15(25.0%)	45(75.0%)	0.531
	Urban	27(29.7%)	64(70.3%)	
Employment status	Employed	14(27.5%)	37(72.5%)	0.943
	Unemployed	28(28.0%)	72(72.0%)	
Transport to KNH	Private Means	3(16.7%)	15(83.3%)	0.261
	Public Means	39(29.3%)	94(70.7%)	
Residence Awaiting	Home	23(28.0%)	59(72.0%)	0.944
	Away from Home	19(27.5%)	50(72.5%)	
Social support Family	No	5(27.8%)	13(72.2%)	0.997
	Yes	37(27.8%)	96(72.2%)	
Social Support Friends	No	36(26.7%)	99(73.3%)	0.361
	Yes	6(37.5%)	10(62.5%)	
Social Support Charitable Organization	No	41(27.9%)	106(72.1%)	0.899
	Yes	1(25.0%)	3(75.0%)	
Funding	NHIF	34(29.1%)	83(70.9%)	0.526
	Cash and Others	8(23.5%)	26(76.5%)	
Cold chain Maintenance of GCSF	No	3(21.4%)	11(78.6%)	0.576
	Yes	39(28.5%)	98(71.5%)	

The bivariate analysis of the clinical characteristics and neutropenia among participants before treatment with neutropenia is displayed in Table 14. There was a statistically significant relationship between the level of neutropenia among participants and administration of radiotherapy ($p<0.001$).

Table 14: Association between clinical characteristics of participants and levels of neutropenia before treatment with GCSF

Variable	**Category**	**Normal ($>1.5\times10^9$/L) (n=42; 28.8%)**	**Neutropenic ($\leq1.5\times10^9$/L) (n=109; 72.2%)**	**p-value**
Concomitant illness	No	30(28.3%)	76(71.7%)	0.837
	Yes	12(26.7%)	33(73.3%)	
Stage of Cancer	Stage I and II	10(31.3%)	22(68.8%)	0.593
	Stage III and IV	21(26.3%)	59(73.8%)	
	Not Staged	11(28.2%)	28(71.8%)	
Concurrent radiotherapy	**No**	**30(22.6%)**	**103(77.4%)**	**<0.001**
	Yes	**12(66.7%)**	**6(33.3%)**	
MASCC risk indexing	Low Probability	23(24.7%)	70(75.3%)	0.284
	High Probability	19(32.8%)	39(67.2%)	
Received GCSF before	No	6(25.0%)	18(75.0%)	0.737
	Yes	36(28.3%)	91(71.7%)	

4.12.2 Association between chemotherapy regimens and the levels of neutropenia before - treatment with GCSF

Bivariate analysis was carried out to determine whether there was any association between chemotherapy regimens and the level of neutropenia before treatment with GCSF.

Table 15: Association between chemotherapy regimens and the neutrophil counts before - treatment with GCSF

Variable	Category	Normal (>1.5×10^9/L) (n=42; 28.8%)	Neutropenic (≤1.5×10^9/L) (n=109; 72.2%)	p-value
Cisplatin based Regimen	No	29(24.6%)	89(75.4%)	0.093
	Yes	13(39.4%)	20(60.6%)	
Carboplatin based Regimen	No	30(27.3%)	80(72.7%)	0.808
	Yes	12(29.3%)	29(70.7%)	
Cyclophosphamide based Regimen	**No**	**36(31.9%)**	**77(68.1%)**	**0.050**
	Yes	**6(15.8%)**	**32(84.2%)**	
Oxaliplatin Based Regimen	No	37(28.5%)	93(71.5%)	0.659
	Yes	5(23.8%)	16(76.2%)	
Paclitaxel based Regimen	No	39(26.9%)	106(73.1%)	0.216
	Yes	3(50.0%)	3(50.0%)	
Trastuzumab based regimen	No	42(28.4%)	106(71.6%)	0.277
	Yes	0(0.0%)	3(100.0%)	
Gemcitabine Based Regimen	No	41(27.9%)	106(72.1%)	0.899
	Yes	1(25.0%)	3(75.0%)	
Other Regimens	No	40(27.4%)	106(72.6%)	0.536
	Yes	2(40.0%)	3(60.0%)	

At bivariate analysis, there was only statistically significant association between cyclophosphamide-based regimens and the level of neutropenia (Table 15).

4.12.3 Multivariate analysis of independent correlates of neutropenia development pre-treatment with GCSF

Multivariate analysis was done to understand the influence of the predictor variables on the development of neutropenia. Multivariate analysis of factors associated with development of neutropenia before use of GCSF demonstrated that participants receiving concurrent radiotherapy had 6.1 times the odds of developing neutropenia compared to participants who were not receiving concurrent radiotherapy (AOR 6.1, 95% CI 1.9-19.8, p=0.003). Table 16 summarizes the multivariate analysis before treatment with GCSF.

Table 16: Covariates of neutropenia pre-treatment with GCSF

Variable	Category	COR(95% C.I)	p-value	AOR(95% C.I)	p-value
Concurrent radiotherapy	**No**	**6.9(2.4-19.8)**	**<0.001**	**6.1(1.9-19.8)**	**0.003**
	Yes	**Ref**			
Cisplastin based Regimen	No	Ref			
	Yes	0.5(0.2-1.1)	0.097	1.1(0.4-2.9)	0.878
Cyclophosphamide based Regimen	No	Ref			
	Yes	2.5(1.0-6.5	0.061	1.8(0.7-5.0)	0.239

4.12.4 Association between profiles of the participants and levels of neutropenia after treatment with GCSF

Bivariate analysis was done to establish whether there was any association between the patient profiles and the levels of neutropenia after treatment with GCSF as shown in Table 17. Post-administration of GCSF, a statistically significant association between gender and the level of neutropenia was obtained ($p<0.001$). Among the male participants, post-treatment with GCSF, 55.8% still remained neutropenic. Twenty-three percent of the female participants remained neutropenic post-treatment with GCSF (Table 17).

Table 17: Association between profiles of the participants and levels of neutropenia after treatment with GCSF

Variable	Category	Normal ($>1.5\times10^9$/L) (n=102; 67.5%)	Neutropenic ($\leq1.5\times10^9$/L) (n=49; 32.5%)	p-value
Gender	**Male**	**19(44.2%)**	**24(55.8%)**	**<0.001**
	Female	**83(76.9%)**	**25(23.1%)**	
Age	50 and Below	42(73.7%)	15(26.3%)	0.210
	Above 50 Years	60(63.8%)	34(36.2%)	
Age at Diagnosis	50 and Below	49(73.1%)	18(26.9%)	0.191
	Above 50 Years	53(63.1%)	31(36.9%)	
BMI	Underweight +Normal	54(66.7%)	27(33.3%)	0.803
	Obese + Overweight	48(68.6%)	22(31.4%)	
Education level	Primary and below	33(62.3%)	20(37.7%)	0.308
	Secondary and above	69(70.4%)	29(29.6%)	
Religion	Christians	101(68.2%)	47(31.8%)	0.201
	Non-Christians	1(33.3%)	2(66.7%)	
Marital Status	Living With a spouse	68(64.8%)	37(35.2%)	0.269
	Not Living With a spouse	34(73.9%)	12(26.1%)	
Smoking	No	100(67.1%)	49(32.9%)	0.324
	Yes	2(100.0%)	0(0.0%)	
Alcohol use	No	100(67.1%)	49(32.9%)	0.324
	Yes	2(100.0%)	0(0.0%)	
Residence	Rural	39(65.0%)	21(35.0%)	0.587
	Urban	63(69.2%)	28(30.8%)	
Employment status	Employed	33(64.7%)	18(35.3%)	0.594
	Unemployed	69(69.0%)	31(31.0%)	
Transport to KNH	Private Means	10(55.6%)	8(44.4%)	0.247
	Public Means	92(69.2%)	41(30.8%)	
Residence Awaiting	Home	54(65.9%)	28(34.1%)	0.627
	Away from Home	48(69.6%)	21(30.4%)	
Social support Family	No	11(61.1%)	7(38.9%)	0.534
	Yes	91(68.4%)	42(31.6%)	
Social Support Friends	No	93(68.9%)	42(31.1%)	0.307
	Yes	9(56.3%)	7(43.8%)	
Social Support Charitable Organization	No	99(67.3%)	48(32.7%)	0.747
	Yes	3(75.0%)	1(25.0%)	
Funding	NHIF	81(69.2%)	36(30.8%)	0.413
	Cash and Others	21(61.8%)	13(38.2%)	
Cold chain Maintenance of GCSF	No	8(57.1%)	6(42.9%)	0.383
	Yes	94(68.6%)	43(31.4%)	

Bivariate analysis between the clinical characteristics of participants and the levels of neutropenia after administration of GCSF are outlined in Table 18. There were no statistically significant associations demonstrated.

Table 18: Association between clinical characteristics of participants and levels of neutropenia after treatment with GCSF

Variable	**Category**	**Normal ($>1.5\times10^9$/L) (n=102; 67.5%)**	**Neutropenic ($\leq1.5\times10^9$/L) (n=49; 32.5%)**	**p-value**
Concomitant illness	No	71(67.0%)	35(33.0%)	0.819
	Yes	31(68.9%)	14(31.1%)	
Stage of Cancer	Stage I and II	19(59.4%)	13(40.6%)	0.415
	Stage III and IV	54(67.5%)	26(32.5%)	
	Not Staged	29(74.4%)	10(25.6%)	
Concurrent radiotherapy	No	87(65.4%)	46(34.6%)	0.128
	Yes	15(83.3%)	3(16.7%)	
MASCC risk indexing	Low Probability	63(67.7%)	30(32.3%)	0.949
	High Probability	39(67.2%)	19(32.8%)	
Received GCSF	No	14(58.3%)	10(41.7%)	0.293
	Yes	88(69.3%)	39(30.7%)	

4.12.5 Association between chemotherapy regimens and the levels of neutropenia after treatment with GCSF

Bivariate analysis carried out to determine the relationship between the development of neutropenia and chemotherapy regimens post-administration of GCSF demonstrated that carboplatin and cyclophosphamide-based regimens had a statistically significant association with the resolution of neutropenia (p=0.009 and p=0.033, respectively) (Table 19).

Table 19: Treatment regimens associated with the development of neutropenia

Variable	Category	Normal (n=102; 67.5%)	Neutropenic (n=49; 32.5%)	p-value
Cisplatin based Regimen	No	76(64.4%)	42(35.6%)	0.119
	Yes	26(78.8%)	7(21.2%)	
Carboplatin based Regimen	**No**	**81(73.6%)**	**29(26.4%)**	**0.009**
	Yes	**21(51.2%)**	**20(48.8%)**	
Cyclophosphamide based Regimen	**No**	**71(62.8%)**	**42(37.2%)**	**0.033**
	Yes	**31(81.6%)**	**7(18.4%)**	
Oxaliplatin Based Regimen	No	90(69.2%)	40(30.8%)	0.272
	Yes	12(57.1%)	9(42.9%)	
Paclitaxel based Regimen	No	98(67.6%)	47(32.4%)	0.962
	Yes	4(66.7%)	2(33.3%)	
Trastuzumab based regimen	No	100(67.6%)	48(32.4%)	0.974
	Yes	2(66.7%)	1(33.3%)	
Gemcitabine Based Regimen	No	100(68.0%)	47(32.0%)	0.447
	Yes	2(50.0%)	2(50.0%)	
Other Regimens	No	99(67.8%)	47(32.2%)	0.714
	Yes	3(60.0%)	2(40.0%)	

Among the participants on carboplatin-based regimens, 51.2% had resolution of neutropenia post-treatment with GSCF. On the other hand, only 18.4% of the participants on cyclophosphamide-based regimens had persistence of the neutropenia post-treatment with GCSF (Table 19).

4.12.6 Association between the management strategies of neutropenia and the MASCC risk index scores

Bivariate analysis was done to determine any association between the MASCC risk index score and the management of neutropenia. There was no statistically significant association (p=0.863) between MASCC index scoring and the type of management of neutropenia among the patients (Table 20).

Table 20: Association between management of neutropenia and MASCC risk index scoring

Variable	Category	MASCC risk index score		p-value
		Low Probability	High Probability	
Management of Neutropenia	Deferment of next chemotherapy Cycle	11(61.1%)	7(38.9%)	0.863
	Prophylactic use of GCSF before	30(65.2%)	16(34.8%)	
	Prophylactic use of GCSF Post	52(60.5%)	34(39.5%)	

4.12.7 Multivariate analysis of the independent covariates of the level of neutropenia post GCSF administration

To identify the most important correlates for the level of neutropenia, multivariate analysis was conducted. The predictor variables were divided into patient socio-demographics, types of cancers, types of chemotherapy regimens, GCSF (dose, duration, administration, availability, cold-chain storage) and concomitant illnesses. Only variables that had a statistically significant association with the level of neutropenia were included in the analysis (Table 21).

Table 21: Independent covariates of development of neutropenia post GCSF administration

Variable	Category	COR (95% C.I)	p-value	AOR(95% C.I)	p-value
Gender	**Male**	**4.2(2.0-8.9)**	**<0.001**	**5.5(2.3-13.5)**	**<0.001**
	Female	**Ref.**		**Ref.**	
Mean BSA	**Mean (SD)**	**4.1(0.8-20.7)**	**0.092**	**9.2(1.4-61.9)**	**0.022**
Carboplatin based Regimen	**No**	**Ref.**		**Ref.**	
	Yes	**2.7(1.3-5.6)**	**0.010**	**4.3(1.7-10.4)**	**0.003**
Cyclophosphamide based Regimen	No	Ref.		Ref.	
	Yes	0.4(0.2-0.9)	0.037	0.9(0.3-2.0)	0.782

Male participants had 5 times the odds of developing neutropenia compared to female participants (AOR 5.5, 95% CI 2.3-13.5, p <0.001). There was a significant association between BSA and development of neutropenia (AOR 9.2, 95% CI 1.4-61.9, p=0.022) whereby for every unit increase in BSA the odds of developing neutropenia increased by 9 times. Participants on carboplatin-based regimens had 4 times the odds developing neutropenia compared to participants on other chemotherapy regimens (AOR 4.3, 95% CI 1.7-10.4, p=0.003) (Table 21).

CHAPTER 5: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1 Discussion

A total of 151 participants seen at the KNH Oncology outpatient pharmacy formed the study population whose mean age was 54.2 (±12.3) years with female preponderance which is comparable to a study carried out in Kenya in 2019 that demonstrated that majority of the participants were females (19). The findings correlate with a similar study carried out in Zimbabwe in 2021, where the mean age of the cancer patients was 52.14 years with female predominance (41). Studies have indicated that women have better health seeking behavior than men (42) and thus are more likely to visit the hospital.

Previously a research in Nigeria reported that the study population was predominated by females with a mean age of 67 years (43). Related studies in the Indian subcontinent indicated an age range of 60-69 years with majority of them being females (44). A study carried out in Iran, reported a mean age of 49.5 (± 18.02) years with dominance of the female gender (45) while a Californian study done in 2014 had a mean age of 60 years among the participants (46). In South West London, the median age reported was 60 years with approximately 60% of the participants being females (47). Perhaps the advanced age correlates with the age of onset for most cancers. Furthermore, studies have demonstrated that neutropenia becomes more common among those aged ≥65 years (48). Additionally, the participants were younger in the present study because the average life expectancy is lower in Kenya at 67.5 years (49) when compared to the population in the West such as in England where it is at 81.5 years (50).

Approximately two-fifths (43.7%) of the study population was found to have a normal BMI. This correlates with a local study that also found that 40.5% of participants had a normal BMI (19). The implication of this profiling is that normal BMI participants have fewer neutrophil counts than obese participants which increases their likelihood of development of neutropenia as suggested by related studies (51). On the other hand, the mean BSA in the present study was $1.7m^2$ (±0.2), which corroborate with findings in Korea where the mean BSA of the participants was $1.69m^2$ (52). Multivariate analysis demonstrated that a higher BSA was associated with the development of neutropenia. These findings are similar to a study carried out in Texas where it was demonstrated that higher BSA was found to increase the likelihood of neutropenia (OR 3.37,

95% CI: 1.72-6.63) (53). BSA was likely to be an independent risk factor for the development of neutropenia. The reasons for this observation were beyond the objectives of the present study.

The study population comprised mostly of participants (49.7%) who had at least attained secondary level of education. Compared to a study done in India in 2014, a quarter of the study population had not attended any form of formal education (44). Perhaps the difference in proportions could be attributed to the Kenyan government which offers free primary and secondary education and encourages all parents to send their children to school. Indian government only offers free education to children falling in the age group of 6 to 14 years (54).

Christians comprised the majority of study participants (98%). In a study carried out in Nigeria in 2006, the study population was also comprised of Christians (85%) (55). In Zimbabwe, the study population (99%) was also composed of Christians (41). This is because the African continent has demonstrated an upsurge in the number of churches across both rural and urban areas (56) and 70% of the local population are Christians (57).

The study reported that approximately 70% of the participants were living with their spouses. In Zimbabwe, majority of the participants who developed neutropenia were married (41). Studies in India showed that 74.4% of the participants were married (44) while in Nigeria, 95% of the participants were living with their spouses (58). The reason why most of the participants were married was probably because they had surpassed the age of getting married (25-30years).

The study population did not smoke tobacco or consume alcohol. Probably patients are well-informed about the negative repercussions of consumption of these substances when they are sick.

Majority (60%) of the participants of the study came from urban residence because they were coming from Nairobi and Kiambu counties which are near the hospital. The likelihood that participants came from these counties is due to the close proximity to KNH. Similarly, in India 73% of the participants came from urban areas (44).

Majority of the participants (77.5%) were funded by NHIF for their treatment. This finding is similar in the United Kingdom where the National Health Service (NHS) is the major funding body among patients (60).

The most commonly encountered type of cancer among the study participants was breast cancer (35.8%). A study carried out in Kenya in 2019, demonstrated that breast cancer was the most commonly (27.8%) encountered type of cancer amongst neutropenic patients (19). Similarly, in Nepal, breast cancer was the most common (20%) cancer associated with neutropenia development (61). The most likely reason why breast cancer was common among the participants could be attributed to its increased screening and awareness among Kenyan women.

Knowledge of the staging of cancer is essential because management modalities are dependent on the extent or stage of disease. For instance, treatment modalities of localized and early stages of cancer may entail surgical modalities while advanced, metastatic and late stages might need palliative care modalities (62). In the present study, a third of the study population that developed neutropenia was in stage III of their respective cancers. These findings are in tandem with the MONITOR-GCSF study where the participants were in stage III of their respective cancers (63). Most patients were in stage III and IV as has been revealed in related studies where people tend to seek medical attention often when the cancer has progressed to advanced stages (64). The predominant comorbidity among the study participants was hypertension as has been reported by a similar study done in Kenya in 2019 (19).

Bivariate analysis demonstrated that before treatment with GCSF, cyclophosphamide-based regimens were significantly associated with neutropenia ($p=0.050$). According to NCCN guidelines, this regimen has been associated with high risk for neutropenia (12). These findings are similar to a local study that found cyclophosphamide-based ($p=0.007$) regimens were significantly associated with neutropenia (19). Furthermore, cyclophosphamide have been implicated in severe bone marrow suppression associated with its mechanism of action of alkylating DNA (13).

The fourth and second cycles of chemotherapy administration were associated with neutropenia among the study participants. An American study reported that the early stages of chemotherapy were associated with neutropenia (65). The likely reason as to why early stages are associated with neutropenia is because there are no established cytotoxic dose adjustments. However, in the subsequent cycles, dose adjustments of cytotoxic chemotherapy are usually done which reduce the likelihood of severe episodes of neutropenia from occurring.

Chemo-radiotherapy using platinum-based radio-sensitizing regimens has been shown to improve the local control of the cancer as well as improve the patients' well-being. The improvements due to chemo-radiation are attributed to the effect of non-selectivity towards tumor and normal cells. However, the effects on the progenitor cells present as neutropenia (66). Consequently, concurrent radiotherapy administration in the present study was significantly associated with the severity of neutropenia (AOR 6.1, 95% CI 1.9-19.8, p=0.003). In a study carried out in Belgium, patients who were receiving concurrent radiotherapy experienced varying levels of neutropenia (67). Similarly, a study carried out in California found that chemo-radiotherapy was an important risk factor that caused treatment interruption due to neutropenia among the study participants (OR 42.1, p=0.001) (68). Among the study participants who were receiving concurrent radiotherapy, the pelvic region was the most commonly irradiated region. In adults, hematopoiesis occurs in the pelvis and the vertebrae (69).

Studies have suggested that neutropenia is defined by an absolute neutrophil count of $<1.5\times10^9$/L (6). Using this cut-off point, exploration of data before GCSF administration revealed that, 55% of the study population had mild neutropenia while 37.1% and 7.3% had moderate and severe levels, respectively. A related study reported that 3.8%, 0.6% and 6.1% of the study population undergoing cytotoxic chemotherapy had mild, moderate and severe neutropenia, respectively (11). A study done in USA found that 33% and 43% of the participants had mild and moderate neutropenia, respectively while 24% had severe neutropenia (70). The reason for the differences in characterization of the neutropenia development is likely to be attributed to the different cutoff values used in decision making among prescribers. During the study it was found that the clinicians used the neutrophil count cutoff at $\leq2.0\times10^9$/L for classifying the levels of neutropenia which was used by the previous studies. This cut-off point was higher than what we used and hence the varying proportions.

Multivariate analysis demonstrated that male gender was more likely to develop neutropenia. Similarly, studies done in United States (71) and United Kingdom (72) demonstrated that male gender was associated with development of neutropenia. These findings are likely due to the fact that males have lower absolute neutrophil counts than females (72) though further studies are required to ascertain the cause.

During the study, it was observed that prescribers do not conduct the MASCC risk-index scoring to classify patients into high or low probability of developing neutropenia. Reports in USA indicated that the MASCC score was rarely used to classify patients and those who fell in the high probability were associated with worse treatment outcomes (73). However, in the study for USA, one half of the participants were at a high probability of neutropenia (73) while locally low probability predominated (61.6%). The likely reason for this observation could be due to the risk factor of comorbidities, used in the MASCC risk-index scoring system, occurring more commonly in the West putting them at a high probability. Furthermore, the factor of age predisposes the West at a higher probability as this population has a longer life-expectancy (50).

In the present study, prescribers gave GCSF prophylactically post cytotoxic chemotherapy administration. This is in tandem with the current prescribing guidelines on the use of GCSF (12). Furthermore, NCCN guidelines also recommend the use of GCSF prophylactically in patients with high risk for neutropenia development (74).

Management of neutropenia was mainly by the use of GCSF. Studies have documented that GCSF should be dosed at 5 mcg/kg to 10 mcg/kg in neutropenia (75). The average dose of GCSF among the participants was 5.95 mcg/kg (±2.04) per day. In the present study, prescribers did not do weight-based dosing of the GCSF and instead prescribed a standard dose of 300 mcg daily for three days to each patient. The reason why the prescribers may not have done weight-based dosing could have been because the GCSF brand available at the facility at the time of the study came as a pre-filled syringe containing 300 mcg. Hence, to reduce the likelihood of wastage, the prescribers decided to prescribe the entire dose. However, despite the uniformity of doses given, most of the participants had resolution of neutropenia.

The study also revealed that GCSF was given once daily for 3 days to all patients. A large multicenter study revealed that patients who received GCSF for a mean duration of 3.7 and 5.2 days reported neutropenia incidences of 7.3% and 5.3%, respectively (75) suggesting that shorter durations of treatment are associated with increased incidences of neutropenia development.

GCSF is a cold-chain commodity that requires refrigeration at temperatures of 2 to 8°C. The study revealed that majority of the participants did not have access to cold-chain facilities which necessitated them to keep coming daily to the hospital for administration of the drug. This posed

inconvenience to the patients especially for those who came from distant counties. Since GCSF is a polypeptide produced by recombinant DNA technology, absence of cold chain storage can cause deterioration of the product which can lead to failure of management of neutropenia. Deterioration of the product may also cause adverse effects such as hypersensitivity (76) and febrile neutropenia that is an oncologic emergency.

During the study GCSF was out of stock for a period of about two weeks. The study participants were forced to outsource GCSF from private facilities at higher costs. At KNH, GCSF costs Kenyan shillings (Kshs.) 1,235 per vial plus a dispensing fee of Kshs. 20. Therefore, for treatment duration of 3 days it would cost Kshs. 3,765. Compared to private facilities such as Nairobi Hospital where GCSF costs Kshs. 1,961 per vial, therefore 3-day duration of treatment would cost Kshs. 5,883. Nairobi Hospital charges Kshs. 154 for an ice pack in case the patient needs one while KNH does not charge for it. Studies have demonstrated that drug stock outs negatively impact on patient healthcare and create distrust (74).

KNH charges Kshs. 4500 for a cool box which can store the drug for an average of 10 hours only. The cool box is only purchased once and can be used in each occasion as needed. NHIF insurance does not cover for this cool box which implies an added cost from the patients' pocket. However, a pegylated form of GCSF is available commercially that requires a single dose of administration rather than the 3-day course of treatment with the standard GCSF. The pegylated form of GCSF available locally costs Kshs. 15,600 for a dose. Hence, the pegylated form of GCSF would be 5 times the cost of the standard GCSF which would not be pocket-friendly to most participants as they are not formally employed. The NHIF cover is based on the hospital formulary and for the medicines required only. This is controlled by the drug availability at the hospital. NHIF provides a cover for up to Kshs. 25,000 and Kshs. 150,000 for first-line and second-line chemotherapy, respectively. Therefore, if the pegylated form of GCSF was available at KNH, NHIF would cover for it alongside other anticancer medications up to the suggested financial limit. This would consequently reduce the inconvenience of coming daily for 3 days for GCSF administration as well as reduce the inadequate handling by the patients.

Bivariate analysis revealed that participants who were on carboplatin-based ($p=0.009$) and cyclophosphamide-based ($p=0.033$) regimens had resolution of neutropenia after treatment with GCSF. A multicenter phase II clinical trial demonstrated that patients who were on

cyclophosphamide, carboplatin and cisplatin-based regimens and received GCSF after chemotherapy administration had a significant difference in the incidence of neutropenia. In this trial, neutropenia incidence drastically reduced from 55% in the placebo group to 7.7% in the GCSF group (77). This demonstrates that GCSF is effective in the management of neutropenia due to these chemotherapies.

Post treatment with GCSF, there was male predominance in the number of patients who remained neutropenic ($p<0.001$). This finding concurs with a study done in USA, where it was also observed that the absolute neutrophil counts were lower in the male participants than females post treatment with GCSF (78). The reason for this observation is likely to be attributed to the fact that males have less neutrophil counts than females due to hormonal differences especially due to estrogen. Absolute neutrophil counts fluctuate during the menstrual cycle among females with increased neutrophil counts observed with higher estradiol levels in serum. Estradiol has been shown to increase hematopoiesis by stimulating enzymes involved in the production of neutrophils (79). Therefore, when GCSF is used in females, a higher increase in the absolute neutrophil counts is likely to be observed compared to males.

5.2 Study limitations

This was a cross-sectional study where the predictor and outcome variables were assessed simultaneously for a short period of time and therefore, it may not reflect what was occurring throughout the year. Additionally, there was missing information such as staging of the cancer as neither did the patients nor the files provided this information.

This study did not establish the cumulative doses and duration of chemotherapy used. Cumulative chemotherapy doses may have an impact on neutropenia. Further, patients who were receiving concurrent radiotherapy were on their last sessions and getting their neutrophil counts post-GCSF administration was difficult. This was because after the radiotherapy they were discharged through other clinics and hence a follow up on them was not possible.

5.3 Conclusion

There was female preponderance in the study. However, male gender was significantly associated with the development of neutropenia. Participants generally had a normal BMI but higher BSA was significantly associated with neutropenia. Neutropenia among the participants

was significantly associated with carboplatin-based regimens and among those receiving concurrent chemo-radiotherapy.

Participants had mild neutropenia pre-GCSF although it tremendously improved on treatment. All participants received a uniform dose of GCSF administration post-chemotherapy but this showed a significant improvement in neutropenia. NHIF was the major funding body among the participants but the storage and handling of GCSF was inadequate as it was not uniform across the participants. Inadequate handling and storage of GCSF was contributed by lack of financing.

5.4 Recommendations

5.4.1 Recommendations on policy and practice

Clinicians should be aware that some patient profiles are associated with neutropenia. Males especially with higher BSA and also undergoing concurrent chemo-radiotherapy are more likely to develop neutropenia and need treatment intensification. In addition, utilization of certain chemotherapy regimens such as carboplatin-based regimens is associated with neutropenia. Therefore, patients on these regimens need strict monitoring on their absolute neutrophil counts and prophylactic use of GCSF. Clinicians should be encouraged to continue prescribing GCSF post-chemotherapy administration because this study has shown that it is effective in the management of neutropenia.

Patients should be encouraged to access other sources of funding, such as patient support groups, as NHIF was not sufficient to cater for all the cancer treatment expenses such as buying cool boxes to improve the storage and handling of GCSF. In addition, the funding should be able to improve the handling and storage of GCSF such as provision of cool boxes. This study suggests perhaps the hospital should procure the pegylated forms of GCSF which may be more expensive but has fewer restrictions on storage and dosing. The pegylated forms of GCSF could reduce patient inconvenience especially for those coming from distant counties. KNH should also seek to procure cool boxes for patients.

KNH should also explore mechanisms that can improve the handling and storage of GCSF such as providing temporary accommodation services for patients travelling from distant counties. This can improve their compliance to treatment and also provide a source of income generation for the hospital.

5.4.2 Recommendations on future areas of research

Additional studies are needed to determine the trends in neutrophil counts recovery after administration of GCSF over time. This will help in determining the efficacy of GCSF over a period of time in the local population.

A study needs to be conducted to find out the effect of the recommended dose and extended duration of GCSF use for the management of neutropenia. This will aid in establishing the optimal duration of treatment and dose for Kenyans.

A large similar study with a wider selection of the types of cancers and cytotoxic chemotherapy regimens needs to be conducted over an extended duration in order to provide a better understanding on the multiplicity of factors associated with the severity of neutropenia.

A study is needed to determine why males with a high BSA have been associated with neutropenia in the Kenyan population. It can provide an insight on whether lifestyle or genetic makeup has an influence.

5.5 New knowledge generated from the study

The study revealed the following:

1. Patient profiles such as male gender, with high BSA and use of carboplatin-based regimens are associated with severe neutropenia among cancer patients.
2. Concurrent chemo-radiotherapy is significantly associated with neutropenia among cancer patients.
3. Concomitant illnesses are not significantly associated with the development of neutropenia among cancer patients.
4. Prophylactic use of GCSF post-administration of cytotoxic chemotherapy is effective in the management of neutropenia

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APPENDIX

APPENDIX 1: ELIGIBILITY CHECKLIST

CRITERIA	YES	NO
Adult cancer patient	☐	☐
On cytotoxic chemotherapy	☐	☐
Patient attends hemato-oncology clinic	☐	☐
Patient with neutropenia confirmed by availability of recent blood works	☐	☐

If patient is excluded, specify reasons for exclusion

……

……

……

APPENDIX 2: DATA COLLECTION FORM
DATE OF DATA COLLECTION: _____ CODE: _____

PART A: PARTICIPANT SOCIODEMOGRAPHICS

1. Date of birth: Date……Month……Year……
2. Age (in years) at diagnosis of cancer: ……
3. Gender: 0 ☐ Male 1 ☐ Female
4. Weight (in kgs): ……
5. Height (in meters): ……..
6. Area of residence: 0 ☐ Urban 1 ☐ Rural
7. Employment: 0 ☐ Employed 1 ☐ Unemployed 2 ☐ Self-employed
8. County: ……..
9. Mode of transport to K.N.H: 0 ☐ Public means 1 ☐ Private means 2 ☐ Foot
   3 ☐ Others (specify): …….
10. Residence of patient while awaiting chemotherapy: 0 ☐ Home 1 ☐ Relative or friends place 2 ☐ Lodges and hotels 3 ☐ KNH
    4 ☐ Others (specify) ……..
11. Level of education (select one): 0 ☐ Primary school 1 ☐ Secondary school
    2 ☐ College 3 ☐ University 4 ☐ Not attended any formal education
12. Social support: 0 ☐ Family 1 ☐ Friends 2 ☐ Charitable organization
13. Mode of funding treatment: 0 ☐ Cash 1 ☐ NHIF 2 ☐ Private Insurance
    3 ☐ Others (specify): ……
14. Denomination: 0 ☐ Christian 1 ☐ Catholic 2 ☐ Muslim 3 ☐ Asian
    4 ☐ Others (specify): ……
15. Marital status: 0 ☐ Single 1 ☐ Married 2 ☐ Divorced
    3 ☐ Widow/Widower 4 ☐ Separated
16. Does the participant smoke? 0 ☐ Yes 1 ☐ No
17. Does the participant drink alcohol? 0 ☐ Yes 1 ☐ No

PART B: CLINICAL CHARACTERISTICS OF PRESENTING CANCER

18. Type of cancer patient has been diagnosed with:

Type of cancer	Tick as appropriate
0Breast cancer	
1Prostate cancer	
2Cervical cancer	
3Esophageal cancer	
4Colorectal cancer	
5Hodgkin's lymphoma	
6Non-Hodgkin's lymphoma	
7Lung cancer	
8Bladder cancer	
9Bone cancer	
10Head and neck squamous cell carcinoma	
11Melanoma	
12Ovarian cancer	
13Pancreatic cancer	
14Others (specify)	

19. Stage of the cancer patient is in? 0 ☐ I 1 ☐ II 2 ☐ III 3 ☐ IV

20. Concomitant illnesses the patient has:

Concomitant illness	Tick as appropriate	Duration (in months)
0Hypertension		
1Diabetes mellitus		
2Dyslipidemia		
3HIV/AIDs		
4Tuberculosis		
5Kidney failure		

6Asthma		
7Arthritis		
8Thyroid disorder		
9COPDs (bronchitis, emphysema)		
10Depression		
11Others (specify)		

PART C: CANCER TREATMENT MODALITIES

21. Cancer chemotherapy regimen patient is on

Chemotherapy regimen (Drugs)	**Doses**	**Duration**	**Current cancer chemotherapy cycle number**

22. Is patient on receiving any radiotherapy concurrently? 0 ☐ Yes 1☐ No

23. If yes, how many sessions of radiotherapy? ……

24. Which site is being radiated? ……..

25. What is the dose of the radiotherapy? ……

26. Other concurrent treatments such as surgery or others ……..

PART D: MANAGEMENT OF NEUTROPENIA

27. What intervention did the prescriber take to manage the neutropenia?

0☐ Prophylactic use of GCSF before cancer chemotherapy administration

1 ☐ Prophylactic use of GCSF post-cancer chemotherapy administration (48hrs)

2 ☐ Chemoprophylaxis using antimicrobials

3 ☐ Manage the neutropenia using antimicrobials once it is diagnosed

Which antimicrobials? 0 ☐ Antibiotics 1 ☐ Antifungals 2 ☐ Antivirals

3 ☐ Antiprotozoals 4 ☐ Others (specify): ……..

4 ☐ Reduce the dose of the anticancer suspected to cause the neutropenia

5 ☐ Change the cancer chemotherapy regimen

7 ☐ Hospitalize the patient in isolation

8 ☐ Defer the next chemotherapy cycle until the neutrophil counts rise significantly

9 ☐ Blood transfusion

10 ☐ Others (specify) ……..

28. What is the MASCC risk-index score in the patient?

Factor	**Weight**	**Patient score**
0Burden of febrile neutropenia with no or mild symptoms	5	
1No hypotension (systolic B.P >90mmHg)	5	
2No chronic obstructive pulmonary disease	4	
3Solid tumor or hematological malignancy with no previous fungal infection	4	
4No dehydration requiring parenteral fluids	3	
5Burden of febrile neutropenia with	3	

moderate symptoms		
6Outpatient status	3	
Age <60 years	2	
Total		

29. What was the prescribers MASCC risk-index score?…….. (put value)

PART E: INFORMATION ABOUT GCSF

30. Dose: …….
31. Duration: ……..
32. Does patient own a refrigerator at home? 0 ☐ Yes 1 ☐ No
33. Does the patient have a cool box? 0 ☐ Yes 1 ☐ No
34. Is a health care facility close to participant's home? 0 ☐ Yes 1 ☐ No
35. Did patient receive the GCSF previously prescribed? 0 ☐ Yes 1 ☐ No
36. If no, what was the suspected reason? 0 ☐ Financial reasons 1 ☐ Refused 2 ☐ No knowledge 3 ☐ Time 4 ☐ Others (specify): …….
37. What is the effectiveness of the GCSF in management of the neutropenia in terms of the absolute neutrophil count measurements?

Cycle of cancer chemotherapy	**Pre-GCSF absolute neutrophil counts (cells/µL)**	**Post-GCSF absolute neutrophil counts (cells/µL) after 48 hours**
0 1st cycle		
1 2nd cycle		
2 3rd cycle		
3 4th cycle		
4 5th cycle		
5 6th cycle		

APPENDIX 3: INFORMED CONSENT FORM -ENGLISH VERSION

A Consent form for cancer patients who visit the outpatient oncology department, and patients invited to willingly participate in the research on the assessment of the treatment of neutropenia using granulocyte colony-stimulating factors

The title of this research is "Assessment of the management of neutropenia with granulocyte colony-stimulating factors among adult cancer patients receiving cancer chemotherapy at Kenyatta National Hospital"

Principal Investigator's Name: DR. BABRA ANITA

Organization Name: UNIVERSITY OF NAIROBI

This form has two sections:

- **An information section to describe information about this study**
- **A certificate of consent form for your voluntarily participation if you agree to participate**

I will give you a copy of this consent form

PART I: Information Section

Introduction

My name is Dr. Babra Anita, studying for a Master degree in clinical pharmacy at the University of Nairobi. I am doing a research on neutropenia, a side effect of cytotoxic chemotherapy, which is very common among cancer patients in Kenya. I am going to describe to you information and invite you to participate in this research. You do not have to agree today whether you will or will not participate in this research. Before you make a decision, you can speak to anybody that you are comfortable with about this research. It is likely that they are words and areas that you may not understand. Kindly do not hesitate to stop me where you do not understand as we proceed and I will take the time to make sure you understand by explaining. You are free to ask me any questions that may arise later even,

Aim of the research

Neutropenia is a common side effect of receiving cancer medications. Neutropenia occurs when the army of your body is defeated and enemies such as bacteria invade the body. Medicines have been developed that manage this side effect. The purpose of carrying out this research is to determine whether the medicines that have been developed are working. We want to know what factors that you as a patient may be having contribute to the management of this side effect.

Type of Research Intervention

This study will only entail an interview from you as a patient. I shall only ask you a few questions to aid me in collecting information for the research.

Selection of participant

We are engaging all adult patients with cancer who will attend the outpatient oncology clinic and develop the side effect of neutropenia to take part in this study.

Voluntary Participation

For you to take part in this research is entirely voluntarily. Whether you choose to participate or not is your own choice. All the medical services you get from this clinic will continue to be provided to you and nothing is expected to change whether you choose to take part or not. Later you may decide to change your mind and quit taking part even though you had previously agreed.

B. Description of the Process

I shall have identified you from your treatment file and then proceeded to ask from you a few questions regarding your current treatment and your financial capabilities.

Duration

The study takes place over duration of 5 months. I would like to question you only once to collect the necessary information I need.

Side Effects

You shall experience no side effects as this is an interview only.

Risks

There are no risks that you will experience as this is an interview only.

Benefits

There may not be any benefit for you but you taking part is likely to help the researchers get the solutions to the research questions they are seeking to answer if you participate in this study. Future generations are likely to use the solutions from this study as there may be no benefit to the society at this point in time of the study.

Reimbursements

You will not be provided with any monetary incentives or gifts to participate in this study

Confidentiality

While conducting this study in your community setting, "something out of the ordinary" will be done. With you participating in this study, it is likely that other people in your community will become aware

that you are taking part and you may be asked questions from them. We, as researchers, will not disclose the identity of all those taking part in this study.

Any information we shall collect from this study will be kept in utmost confidentiality. Information that will be collected related to you during the study will be kept away and only myself will be able to access it. We shall be using numbers instead of your name with regards to any of your information. Only the researchers are aware of your number and all the information will be locked using a lock and key. This information shall not be disclosed to anybody except me.

Results sharing

Knowledge acquired from conducting this study will be shared to you by holding community gatherings before it is revealed and made available to the general public. The information that will not be shared is the confidential information. The hospital will hold small meetings where the research findings will be distributed. We will then publish the findings after holding these meetings so that other healthcare workers may also be educated from this study.

Right to Refuse or Withdraw

If you do not wish to participate in this research, you are not compelled to do so and refusal to participate will not disrupt in any way your medical treatment at this clinic. You will still continue to have all the services that you usually receive at this clinic. You may quit taking part in this study at any point in time that you wish to do so and will not lose any of your patient rights here. Your medical treatment will not affected in aspect in this clinic.

Contact person

If you have any queries or questions regarding your participation in this study, you may ask them today or later, even after the study has already began. If you wish to ask questions at a later date, you do not have to hesitate to contact and speak with the following: DR. BABRA ANITA (+254 702624422, P.O.Box 7567-00300 Nairobi, babraanita60@gmail.com)

This study has been reviewed and approved by the Kenyatta National Hospital-University of Nairobi Ethics and Research Committee (KNH-UoN-ERC), which is a committee whose task it is to make sure that research participants are protected from harm. If you wish to find about more about the KNH-UoN-ERC, contact 2726300 ext. 44102, email uonknh_erc@uonbi.ac.ke

You can ask me any more questions about any part of the research study, if you wish to. Do you have any questions or clarifications?

PART II: Certificate of Consent

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

Name of Participant_____

Signature of Participant _____

Date _____

Day/month/year

If illiterate

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Name of witness_____ AND Thumb print of participant

Signature of witness _____

Date _____

Day/month/year

Statement by the researcher/person taking consent

I have read out accurately the information sheet to the potential participant, and to the best of my ability made sure that the participant has understood that only an interview will be carried out.

I hereby confirm that the participant was given an opportunity to ask questions freely about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given voluntarily and freely.

A copy of this form has been provided to the participant.

Name of Researcher/person taking the consent: DR.BABRA ANITA

Signature of Researcher /person taking the consent_____

Date _____

Day/month/year

KIAMBATISHO 3: IDHINI YA HABARI – KISWAHILI VERSION

Fomu ya idhini ya habari ya wagonjwa wa saratani ambao huudhuria kliniki ya wagonjwa wa nje,katika idara ya onkolojia , na ambao tunakaribisha kushiriki katika utafiti kuhusu kutathmini matibabu ya upungufu wa chembe chembe kutumia granulocyte colony-stimulating factors.

Kichwa cha mradi wa utafiti ni Assessment of the management of neutropenia with granulocyte-colony stimulating factors among adult cancer patients receiving cancer chemotherapy at Kenyatta National Hospital.

Jina la Mpelelezi Mkuu: DR. BABRA ANITA

Jina la Shirika: CHUO KIKUU CHA NAIROBI

Fomu hii ya idhini ina sehemu mbili:

- **Karatasi ya habari (kukueleza habari kuhusu utafiti)**
- **Cheti cha Idhini (ya sahihi iwapo utakubali kujihusisha na utafiti huu)**

Utapewa nakala ya fomu yote ya idhini ya habari

SEHEMU I: Karatasi ya Habari

Utangulizi

Mimi ni Dr. Babra Anita, mwanafunzi wa Shahada ya uzamili ya Clinical Pharmacy katika Chuo Kikuu cha Nairobi.Ninafanya utafiti kuhusu upungufu wa chembe chembe ya kupigana na maradhi kwa damu ,mathara yanayotokana na matibabu ya saratani na ambayo ni kawaida sana miongoni mwa wangojjwa wa saratani nchini Kenya.Nitakupa habari na kukukaribisha ujiunge katika utafiti huu. Kabla ya kufanya uamuzi wowote,unaweza kuzungumza na rafiki yeyote kuhusu utafiti huu. Huenda kuna maneno ambayo hutayaelewa.Tafadhali nijulishe nisite nitakapokuwa nikikuelezea habari hii na nitachukua muda kukuelezea.Iwapo utakuwa na maswali baadaye,usione shaka kuniuliza.

Kusudi la utafiti

Neutropenia iko miongoni mwa madhara ya kawaida unapopokea matibabu ya saratani. Upungufu wa chembe chembe hutokea iwapo jeshi la mwili limeshindwa na maadui kama bakteria wanavamia

mwili.Madawa ya kudhibiti adhari hii yameendelezwa.Sababu ya kufanya utafiti huu ni kuweza kujua kama madawa ambayo yameendelezwa yanafanya ipasavyo.Tunataka kujua ni sababu zipi ambazo wewe kama mgonjwa unachangia katika kukumbana na adhari hii.

Aina ya utafiti

Utafiti huu utahusisha mahojiano pekee kati ya mhusika na wewe kama mgonjwa.Nitakuuliza maswali chache ambayo yatanisaidia kupata habari itakayotumiwa katika utafiti.

Uchaguzi wa mshiriki

Kila mgonjwa ambaye ni mtu mzima na anayehudhuria kliniki yetu ya wagonjwa wa nje na akapata adhari ya kando ya neutropenia anakaribishwa kujiunga na utafiti huu.

Ushiriki wa hiari

Ushiriki wako katika utafiti huu ni wa hiari.Ni chaguo lako kujiunga na utafiti huu au la. Iwapo utachagua kujiunga au kutojiunga na utafitu huu,utaendelea kupokea huduma zote katika kliniki hii bila mabadiliko yoyote. Unaruhusiwa kubadili uamuzi wako baadaye na kuacha kushiriki hata kama ulikubali kabla.

B.Maelezo ya mchakato

Nitakuchagua kutoka kwa faili yako ya matibabu kisha nitakuuliza maswali chache kuhusu matibabu yako na pia hali yako ya kifedha.

Muda

Utafiti huu utachukua jumla ya miezi tano. Ningependa kukutana nawe mara moja pekee ili nipate habari ya lazima ninayohitaji.

Madhara

Hakuna madhara yoyote yatatokana kwani haya ni mahojiano tu.

Hatari

Hakuna hatari itatokana kwani haya ni mahojiano tu.

Faida

Iwapo utashiriki katika utafiti huu, huenda hakutakuwa na faida yoyote kwako lakini huenda ushiriki wako utatusaidia kupata jibu la swali linaloulizwa katika utafiti huu.Huenda hakutakuwa na faida yoyote kwa jamii katika hatua hii ya utafiti, lakini vizazi vya baadaye huenda vikafaidika.

Malipo

Hutapatiwa pesa wala zawadi kujiunga na utafiti huu.

Usiri

Utafiti huu ni kitu geni katika jamii yako.Kuna uwezekano kuwa iwapo wengine katika jamii watafahamu kuwa unashiriki,wanaweza kuuliza maswali.Hatutatambulisha washiriki wa utafiti huu.

Habari tutakazopata kutokana na utafiti huu zitahifadhiwa kwa kisiri.Habari kukuhusu zitakazopatikana kutokana na utafiti huu zitahifadhiwa na hakuna yeyote isipokuwa watafiti wataweza kuiona.Habari zozote kukuhusu zitatumia nambari badala ya jina lako.Watafiti pekee ndio watajua nambari yako na habari hizo zitatiwa kufuli.Hakuna yoyote isipokuwa mimi atajulishwa habari hizo.

Kugawana matokeo

Maarifa tutakayopata kutokana na utafiti huu yatajulishwa kwako kupitia mikutano ya kijamii kabla ya kujulishwa kwa upana kwa umma.Habari za kisiri hazitatolewa.Kutakuwa na mikutano midogo katika hospitali ambapo matokeo ya jumla ya utafiti yatajulishwa kwenu.Baada ya mikutano hii, matokeo yatachapishwa ili watu wenye nia wapate kujifunza kutokana na utafiti huu.

Haki ya Kukataa au Kujiondoa

Sio lazima ushiriki katika utafiti huu na iwapo utakataa , matibabu yako katika kliniki hii hayatadhurika kwa njia yeyote.Bado utapata faida zote zile ambazo ungepata .Unaweza kuwacha kushiriki katika utafiti huu wakati wowote bila kuhofia kuwa utapoteza haki zako kama mgonjwa huku.Matibabu yako katika kliniki hii hayatadhurika kwa vyovyote vile.

Nani wa Kuwasiliana naye

Iwapo una maswali yoyote, unaweza kuyauliza sasa au baadaye, hata baada ya utafiti kuanza.Iwapo utataka kuuliza maswali baadaye,unaweza kuwasiliana na: DR. BABRA ANITA (+254702624422, P.O.Box 7567-00300 Nairobi, babraanita60@gmail.com)

Pendekezo hili limepitiwa upya na kuadhinishwa na Kenyatta National Hospital-University of Nairobi Ethics and Research Committee (KNH-UoN-ERC), ambayo ni kamati lenye jukumu la

kuhakikisha kuwa washiriki wa utafiti wamekingwa kutokana na madhara.Iwapo utataka kujua mengi kuhusu KNH-UoN-ERC, wasiliana nao katika nambari 2726300 ext. 44102, barua pepe uonknh_erc@uonbi.ac.ke

Unaweza kuniuliza maswali ya ziada kuhusu sehemu yoyote ya utafiti huu,iwapo utataka.Una maswali yoyote?

Sehemu II: Cheti cha Idhini

Nimesoma habari zinazotangulia,au nimesomewa. Nimepata fursa ya kuuliza maswali kuihusu na maswali yote niliyouliza yamejibiwa nikaridhika.Nakubali kwa hiari kushiriki katika utafiti huu.

Jina la Mshiriki_____

Sahihi ya Mshiriki_____

Tarehe_____

Siku/mwezi/mwaka

Kama hujui kusoma na kuandika

Nimeshuhudia usomaji sahihi wa fomu ya idhini kwa mshiriki mtarajiwa, na mshiriki amepata fursa ya kuuliza maswali.Nathibitisha kuwa mshiriki ametoa idhini kwa uhuru.

Jina la Shahidi_____ NA Alama ya kidole ya mshirika

Sahihi ya Shahidi_____

Tarehe_____

Siku/mwezi/mwaka

Kauli ya mtafiti/mtu anayeomba idhini

Nimemsomea mshiriki mtarajiwa karatasi ya habari kwa usahihi, na nimehakikisha kwa uwezo wangu wote kuwa mshiriki anaelewa kuwa mahojiano pekee ndio yatatokea.

Nathibitisha kuwa mshiriki alipewa fursa ya kuuliza maswali kuhusu utafiti huu , na kuwa maswali yote yamejibiwa kwa usahiihi na kwa uwezo wangu wote.Nathibitisha kuwa mshiriki hajalazimishwa kupeana idhini, na idhini amepeana kwa uhuru na hiari.

Mshiriki amepewa nakala ya fomu ya idhini ya habari.

Jina la Mtafiti/mtu anayeomba idhini : DR. BABRA ANITA

Sahihi ya mtafiti/mtu anayeomba idhini_____

Tarehe_____

Siku/mwezi/mwaka

APPENDIX 4: COUNTIES OF PARTICIPANTS

County	Bungoma	1	0.7
	Embu	3	2.0
	Garissa	1	0.7
	Homabay	1	0.7
	Huruma	1	0.7
	Kagundo	1	0.7
	Kajiado	7	4.6
	Kakamega	3	2.0
	Kangundo	1	0.7
	Kiambu	**26**	**17.2**
	Kirinyaga	4	2.6
	Kisii	6	4.0
	Kisumu	4	2.6
	Kitui	8	5.3
	Machakos	6	4.0
	Makueni	7	4.6
	Meru	4	2.6
	Migori	1	0.7
	Murang'a	**13**	**8.6**
	Nairobi	**30**	**19.9**
	Nakuru	2	1.3
	Nandi	1	0.7
	Narok	1	0.7
	Nyamira	1	0.7
	Nyandarua	5	3.3
	Nyeri	**11**	**7.3**
	Siaya	1	0.7
	Uasin Gishu	1	0.7

APPENDIX 5: KNH-UoN ERC APPROVAL LETTER

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
Tel:(254-020) 2726300 Ext 44355

KNH-UON ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

KENYATTA NATIONAL HOSPITAL APPROVED 21 JAN 2021 KNH/UoN-ERC P. O. BOX 20723 - 00202 NAIROBI

Ref: KNH-ERC/A/22

21 January 2021

Dr. Anita Babra
Reg. No.U56/35897/2019
Dept. of Pharmaceutics and Pharmacy Practice
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Dr. Babra

RESEARCH PROPOSAL – ASSESSMENT OF TH E MANAGEMENT OF NEUTROPENIA WITH GRANULOCYTE COLONY STIMULATING FACTORS AMONG ADULT PATIENTS RECEIVING CANCER CHEMOTHERAPY AT KENYATTA NATIONAL HOSPITAL (P598/10/2020)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above research proposal. The approval period is 21st January 2021 – 20th January 2022.

This approval is subject to compliance with the following requirements:

a. Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b. All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH-UoN ERC before implementation.
c. Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d. Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e. Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
f. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
g. Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

For more details consult the KNH- UoN ERC website **http://www.erc.uonbi.ac.ke**

Yours sincerely,

PROF. M. L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Senior Director, CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information Dept, KNH
The Dean, School of Pharmacy, UoN
The Chair, Dept. of Pharmaceutics and Pharmacy Practice, UoN
Supervisors: Dr. David G. Nyamu, Dept. Pharmaceutics and Pharmacy Practice, UoN
Dr. David E. Wata, Division of Pharmacy, KNH

APPENDIX 6: INSTITUTIONAL APPROVAL

KNH/R&P/FORM/01

KENYATTA NATIONAL HOSPITAL
P.O. Box 20723-00202 Nairobi

Tel.: 2726300/2726450/2726565
Research & Programs: Ext. 44705
Fax: 2725272
Email: knhresearch@gmail.com

Study Registration Certificate

1. Name of the Principal Investigator/Researcher
   DR: BARRA ANITA
2. Email address: babraanita66@gmail.com Tel No. 0702624433
3. Contact person (if different from PI).. N/A
4. Email address: ...N/A... Tel No. N/A
5. Study Title
   ASSESSMENT OF THE MANAGEMENT OF NEUTROPENIA WITH GRANULOCYTE COLONY STIMULATING FACTORS AMONG ADULT PATIENTS RECEIVING CANCER CHEMOTHERAPY AT KENYATTA NATIONAL HOSPITAL
6. Department where the study will be conducted ONCOLOGY PHARMACY
   (Please attach copy of Abstract)
7. Endorsed by KNH Head of Department where study will be conducted.
   Name: DR A.R BIRUCH Signature ABiruch Date 27/01/2021
   CHIEF PHARMACIST KENYATTA NATIONAL HOSPITAL
8. KNH UoN Ethics Research Committee approved study number P593/10/2020
   (Please attach copy of ERC approval)
9. I DR: BABRA ANITA commit to submit a report of my study findings to the Department where the study will be conducted and to the Department of Medical Research.
   Signature..... Date 27/01/2021
10. Study Registration number (Dept/Number/Year) Pharmacy/49/2021
    (To be completed by Medical Research Department)
11. Research and Program Stamp

KENYATTA NATIONAL HOSPITAL
27 JAN 2021
P.O. Box 20723 - 00202 NRS
Research Resource Centre

All studies conducted at Kenyatta National Hospital must be registered with the Department of Medical Research and investigators must commit to share results with the hospital.

Version 2: August, 2014